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The Stress Response, Psychoeducational Interventions and Assisted Reproduction Technology Treatment Outcomes: A Meta-Analytic Review

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The Stress Response, Psychoeducational Interventions and Assisted

Reproduction Technology Treatment Outcomes: A Meta-Analytic Review

by

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of the requirements for the degree of
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DEDICATION

     This work is dedicated to my family who has educated me in the truly worthwhile things in life. To Mark, my husband, to whom I owe so much. It is through his patience, love, and support that this achievement was possible. To my parents, Robert P. and Margaret Hutcheson, who have given guidance and encouragement throughout my life, as a token of love, gratitude, and respect. To my sisters, Sandra and Rebecca, whose friendship and companionship I cherish. In loving memory to my grandmother, Viola Rose, whose example through life and humor has inspired me daily to become a better daughter, sister, wife, and woman.

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If I have seen farther than others, it is because I stood on the shoulders of giants.
-Isaac Newton

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ABSTRACT

The psychological impacts of infertility have been well documented in the literature, providing evidence to support that at least some women who confront infertility are at risk for heightened distress and depressive symptoms. In response to this accumulated evidence, it has been argued that psychoeducational interventions may provide an important component to the treatment of infertility. While several theoretical models postulate the effects of stress on infertility treatment outcomes, results of these investigations have led to conflicting conclusions. However, a synthesis of the accumulated data examining the effects of stress on ART treatment outcomes was nonexistent until the conduct of this study. Therefore, the purpose of this study was to investigate the impact of stress on ART treatment outcomes and to determine whether psychoeducational interventions mitigate the impact of stress experienced by women during an ART treatment program. Two hypotheses were tested: 1. Increased levels of stress will be associated with a lower likelihood of Assisted Reproductive Technology (ART) treatment success, and 2. Psychoeducational interventions will mitigate the effects of stress experienced during Assisted

Reproductive Technology (ART) treatment. A meta-analysis analyzing the

results for each hypothesis was tested through a hierarchical linear regression

model. A total of 13 studies, representing 43 effect sizes, were included in the

analysis investigating the relationship between stress and ART treatment

outcomes. Results of the HLM regression model suggest that stress has a small

negative association with ART treatment outcomes (d=0.2012, p< .05). The

analysis investigating the relationship between psychoeducational interventions

and stress included a total of 4 studies, representing 12 effect sizes. Empirical

evidence gathered through this analysis revealed that the effect of

psychoeducational interventions on the stress experienced by women

participating in an ART treatment program were not statistically significant

(d=0.3071, p>.05). However, because this analysis was based on such a small

sample of studies, generalizations regarding the efficacy of psychoeducational

interventions cannot be made. Therefore, research aimed at investigating the

impacts of a variety of programs should continue in an effort to provide more

conclusive information.

CHAPTER ONE: INTRODUCTION

Stress is a common part of life and has come to describe a myriad of events or circumstances in a variety of contexts. For many couples, the problem of infertility diagnosis and treatment is one of life's stressful circumstances that they face. The role of stress in infertility research has been a topic of interest for many decades. The field of research in the study of stress and infertility advanced along with technological and medical options in the treatment of infertility. While originally, research focused on whether stress was the cause of infertility, current research focuses on the effects of stress on infertility treatment outcomes. Although medical advancements in the treatment of infertility provides hope for conceiving a child to infertile couples, the plethora of treatment interventions available to couples may also be the source of considerable stress. Recognizing this paradox, many physicians and medical facilities offering Assisted Reproduction Technology services to infertile couples have begun to offer psychoeducational interventions to patients. Only recently has interest in the efficacy of these programs grown.

Stress

Stress is a complex, dynamic interaction between a person and the various conditions, changes, and the demands of his or her life. Stress can be categorized as either acute or chronic. Acute stress is a short-lived response to

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a one-time incident or event that usually comes and goes quickly. Its effects can last from minutes or hours to days or weeks. Chronic stress is caused by a continuing string of stressful incidences, or an ongoing situation. Stress is experienced in various degrees. Low levels of stress may not even be noticeable while slightly higher levels of stress can be positive by challenging one to act in creative and resourceful ways. However, high levels of stress can be harmful leading to a variety of illnesses and chronic diseases (Millon et al., 1982).

Over the past several decades, the interest in "stress" has increased leading to a number of articles and studies published from medical, physiological, biochemical, sociological, psychological, educational, and even spiritual perspectives (Breznitz & Goldberger, 1993; Selye, 1983). Most theoretical models of stress conceptualize stress as a response elicited by an individual to an event or situation. Models based on theories of stress as a response explain stress as a physiological adjustment process and postulate that stress is an internal response. Selye's (1936) psycho-physiological model, "General Adaptation Syndrome" (GAS), presents stress as a non-specific, physiological response that consists of three sequential stages of alarm, resistance and exhaustion. He later broadened his theory to recognize stress as an internal condition of an individual when faced with environmental stressors. Selye also highlighted that any emotion or activity, whether it produced joy or sadness, causes stress. In addition, he noted that stressful life events often result in disease and unhappiness when individuals are unprepared to cope with these events (Selye, 1993).

Infertility

Fertility is the ability of a man and a woman to reproduce. The epidemiological term, fecundability, refers to the monthly probability of conception without the use of any contraception (Jansen, 1993; Tsaltas, 1997). A couple is said to be subfecund, or infertile, when there is an involuntarily long interval until their first conception or between births. A common definition of infertility is the state in which a couple desiring to have a child cannot conceive after 12 months of unprotected intercourse (Tsaltas, 1997). Failure to conceive after 12 months of unprotected intercourse is taken to be abnormal as 90% of couples will have conceived within that time (Tietze, 1956, 1968; Tsaltas, 1997).

Infertility is either classified as primary or secondary. Primary infertility refers to women who have never achieved pregnancy, whereas, secondary infertility refers to those women who have achieved pregnancy at least once before, regardless of the outcome, and who cannot achieve a subsequent pregnancy (Thonneau et al., 1991; Seibel, 1993; Tsaltas, 1997). Sterility, on the other hand, is the absolute inability to reproduce. When the fecundability of a couple is zero, for whatever reason, the couple is defined as infecund, or sterile (Tsaltas, 1997; Jansen, 1993). Although the true incident rate of sterility is unknown, it is believed that 3-5% of the population is sterile (Spira, 1986; Jansen, 1993, Tsaltas, 1997).

Estimates regarding the actual incidence of infertility, primary and secondary, vary. The sole reliable sources of demographic information about infertility and the use of infertility services in the United States are national

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surveys conducted by the National Center for Health Statistics, the last of which was carried out in 1995 (Seibel, 1993; CDC, 1997). At that time, an estimated 7.1% of married couples, or 2.1 million, in which wives aged 15 to 44 years were infertile. Among all women of reproductive age, 24% of women of reproductive age were surgically sterile. An additional 10.2% (6.1 million) had impaired fecundity (CDC, 1997). The proportion of patients seeking treatment presenting with primary and secondary infertility have remained remarkably constant with 67% to 71% of patients categorized as presenting primary infertility and 29% to 33% presenting with secondary infertility (Hull et al., 1985; Templeton et al., 1991; Thonneau et al., 1991; Tsaltas, 1997).

Social Context of Infertility

For many American couples, raising a family is a major life event for which they have planned as meticulously as they did their education, career, and finances, carefully weighing all factors and waiting for the most opportune time to start a family. Most couples assume that they are in control of their reproduction and that when they are ready to begin their family, they will conceive with ease. Unfortunately, many couples desiring to conceive a child face the problem of infertility. For many years, the incident rate of infertility was expected to range around 10% (Tsaltas, 1997). However, a number of recent studies give a clear indication that the actual incident rate of infertility ranges from 13.5% to 18.4%, which translates to one in seven women. These studies demonstrate that infertility is a common and important health problem (Tsaltas, 1997).

Currently, more than 5 million couples in the United States can be classified as having a substantial infertility-related problem. At least 8% of married couples will be initially unsuccessful in their attempts to have a biological child. The inability to conceive can be the source of considerable trauma and often prolonged stress, which may lead to a series of steps involving medical intervention for those who can afford the expense (Schneider, 2000; Whiteford & Gonzalez, 1995; Menning, 1980; 1982; Pearson, 1992).

While most Americans view parenting as a central life role, American society emphasizes controlling fertility through contraception and on choosing when to have children and raise a family (Pearson, 1992). American society and many of our idealizations when growing up focus on becoming parents and raising children as an expected experience in adult life. According to Cahill and Suchy (1981), the family forms an important part of American social structures and is an integral part of our own identities as individuals. Veevers (1980) and Miall (1985) identify two predominate procreative social norms in American society:

1. All married couples should reproduce, and

2. All married couples should want to reproduce.

These social norms are also supported through American governmental policies that encourage reproduction and reward the image of parenthood through policies such as income tax deductions. Furthermore, Greil (1991) states "…the heart of the experience of infertility appears to lie in the inability to proceed with one's life according to life course norms that are both reinforced by others and

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accepted as valid by the affected individual." In addition to the social affirmation, parenting often involves a confirmation of our sexual identity and feelings of self-worth (Greil, 1991; Shepherd, 1992; Whiteford & Gonzales, 1995).

The Stress of Infertility

While infertility can be a painful and devastating experience for both men and women, their responses are influenced by differential role expectations and socializations. The strong desire to have children and the subsequent responses to infertility have been shaped by our culture through a complex system defined by personal, familial, social, and medical expectations that transcends sex, age, religion, ethnicity, and socio-economic class (Whiteford & Gonzalez, 1995). In American society, much of women's personal and social identity is linked to motherhood. The experiences of pregnancy, childbirth, and motherhood are seen as an intrinsic part of a woman's adult life (Pearson, 1992). In a culture where womanhood is sometimes thought of as synonymous with motherhood, infertility, for many women, carries a stigma borne of shame and secrecy. Despite increasing awareness of the diagnosis and treatment options, infertility remains an "invisible" health issue. Not visible, life threatening, or disfiguring, infertility is often a secret life crisis experienced by couples in isolation (Menning, 1982; Sandelowski & Pollock, 1986; Pearson, 1992; Whiteford & Gonzalez, 1995; Shoener & Krysa, 1996; Greil, 1997).

Shaped by cultural, social, and personal expectations, infertility can create overwhelming stress, which tests a couple's normal coping mechanisms because it is usually unexpected, may be unexplained, and lasts for an indeterminate

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length of time. The diagnosis and attempted treatment of infertility is often an

acute and unanticipated life crisis of considerable proportion for couples. A state

of crisis can be defined as a disruption in the steady state, or a period of

disequilibria. Elements common to a state of crisis include:

- A stressful event occurs that poses a threat that is insoluble in the
  immediate future,

- The problem overtaxes the existing resources of the person(s)
  involved because the remedy or solution is beyond traditional
  problem-solving methods,

- The problem is perceived as a threat to important life goals of the
  person(s) involved, and

- The crisis situation may reawaken unsolved key problems for both
  the near and distant past (Menning, 1980).

In addition, infertility can create a chronic or prolonged state of crisis with no

identifiable solution (Menning, 1980; Boivin et al., 1995; Whiteford & Gonzalez,

1995; Schoener & Krysa, 1996).

Medical developments in the treatment of infertility have led to a "merry-

go-round" of interventions available to those couples that can afford them. Prior

to these developments in medical science, an infertile couple would decide either

to remain childless or to adopt. Today, however, couples have an excessive

number of interventions available to them increasing hope that they will be

successful in achieving and completing a pregnancy. In the current venue of

infertility treatment, couples may choose to undergo years of treatment,

postponing resolution to the life crisis they are experiencing. These

advancements in medical treatment, while offering hope to infertile couples, may

create unrealistic expectations in which infertile couples define themselves not as

childless, but as 'not yet pregnant' (Boivin et al., 1995; Whiteford & Gonzalez,

1995; Schoener & Krysa, 1996; Menning, 1980).

In addition to the emotional stress and responses shaped by societal

expectations, couples have described the medical tests and treatments for

infertility as stressful. When a couple decides on the necessity of seeking

specialized medical attention because of their inability to conceive, the initial

medical interview investigates extremely personal subjects: the couple's sexual

performance, sexual history including the frequency of sexual intercourse,

premarital and extramarital relationships, previous pregnancies including

abortions and miscarriages, attitudes about sex, and usual sexual practices.

These very personal questions can be threatening, embarrassing, intrusive or

demeaning for the couple (Abbey et al., 1992).

The medical treatment and interventions for infertility have been

universally described by patients as painful, embarrassing, and physically,

psychologically and financially draining (Berg & Wilson, 1991; Boivin &

Takefman, 1995; Schneider, 2000). Side effects from medication, recovery from

surgery, and time loss at work due to frequent medical appointments have all

been identified as stressful events by couples. While these experiences are

more devastating for some individuals than for others, the experiences can result

in disrupted relationships, increased social isolation, depression, and increased

hopelessness (Abbey et al., 1992; Domar, et al., 1992; Pearson, 1992; Whiteford & Gonzalez, 1995; Greil, 1997).

The Role of Psychoeducational Interventions in Infertility Health Care

Cognitive therapy is increasingly being accepted as an effective treatment option for depression (Domar et al., 2000). Several studies with cancer patients combined support with cognitive-behavioral techniques. The benefits of this educational model included decreased psychological distress, longer life span, and decreased mortality (Helgeson & Cohen, 1996; Domar et al., 2000). Another study including patients with multiple sclerosis emphasized coping-skills training. This study demonstrated greater advantages in well-being and coping for the patients receiving the coping skills training than those who participated in only a peer telephone support group. Cognitive-behavioral approaches have also been shown through a multitude of studies and investigations to be effective in reducing symptoms of depression and decreasing health costs in patients with a wide variety of conditions including cardiac, abdominal, orthopedic, dental surgery, and invasive medical procedures (Mandle et al., 1996; Domar et al., 2000).

The most common intervention to help couples cope with the stress of infertility in the United States is patient education and social networking through support groups. While the programs designed for couples with infertility vary from program to program, some elements common among all of them include educational programs and emotional supports designed to alleviate symptoms of stress for individuals or couples experiencing infertility. One such program is the

Mind/Body Program for Infertility. Based on the elicitation of the relaxation response exercise, this program follows a 10-week protocol designed to treat individuals experiencing any medical symptoms caused or aggravated by stress. In addition to relaxation-response training, The Mind/Body Program for Infertility and other similar programs include sessions focusing on stress management training and strategies, exercise, discussions and education on nutrition, and group support. Couples participating in cognitive-behavioral therapy are typically introduced to a wide variety of techniques, including relaxation-response training, cognitive restructuring, emotional expression, and nutrition and exercise education relevant to infertility (Domar et al., 1990; 2000; Connolly et al., 1992).

<div align="center">Stress and Infertility Research</div>

Given the developmental salience of reproduction, the intimacy of the situation, and the uncertainty of the outcome, the role stress plays in infertility and infertility treatment has been a common topic of research in the area of reproductive health and medicine. Contemporary studies dominating this area of research encompass four major themes:

1. Does stress cause infertility?

2. Does infertility cause stress?

3. Does infertility treatment cause stress?

4. Does stress affect the success of infertility treatment?

The first area of research, which has a long-standing focus in medical research, explores the possibility that infertility may have psychological causes. These studies are based on the psychogenic hypothesis. The foundation of this model

rests on the assumption that many cases of infertility, especially non-organic infertility, are caused by an unconscious resistance to motherhood on the part of the infertile woman. These earlier studies attempted to show that unconscious conflicts and/or psychological maladjustment caused infertility. While several recent studies provide some support for the psychogenic hypothesis, most researchers now reject the psychogenic hypothesis (Greil, 1997). However, citing the limitations and flaws to previous studies, some researchers have attempted to revive the psychogenic hypothesis in recent years. In addition, at least one team of researchers has argued for an interactive model, as opposed to the current approach, which assumes that infertility must either cause psychological distress or be caused by it (Greil, 1997; Csemiczky et al., 2000).

In addition to these earlier research initiatives, the literature has documented the psychological impact of infertility and infertility treatment. Most contemporary studies examining the relationship between infertility and stress assume that infertility is the source, rather than the cause, of psychological distress known as the psychological consequences hypothesis. The majority of the literature focusing on the experience of infertility is primarily, but not exclusively, qualitative in nature and provides a more complete picture of the experiences of couples facing infertility. The anecdotal evidence about the correlation between infertility and stress as well as the destructive impacts that infertility-related stress can have on the marriage and the couple's quality of life is compelling. The research findings in this area of interest can be divided into studies on the psychological impact on women, men, and couples experiencing

infertility and treatment. This area of research has advanced the field in that much of the qualitative research analyzes the experiences of infertility within its social context, paying special attention to gender roles, family structure and relationships, the effects of the medical establishments, and the importance of assisted reproductive technology (Andrews et al., 1992; Greil, 1997; Hart, 2002).

Growing out of this field of research are studies examining the relationship between stress and outcomes of assisted reproduction technology (ART). Success of ART, defined as a live birth delivery, depends on many factors such as maternal age, type of infertility, and the experience of the medical clinic and staff. Psychological stress and coping styles may also play a role in the success of ART (Klonoff-Cohen et al., 2000). However, results from these studies are varied and the role of psychological factors and the impact of stress on treatment outcomes are yet to be established (Newton et al., 1990; Smeenk et al., 2001; Wilson & Kopitzke, 2002).

As evidence about the stress of infertility and of infertility treatment has mounted, physicians who treat couples with fertility problems have found they need to be concerned not only with the medical and physiological aspects of the problem but also with its psychosocial ramifications. To this end, several interventions have been implemented with patients including, but not limited to, traditional individual psychotherapy, which often emphasize the similarities in psychological responses between infertility and grief work, as well as support groups that allow the couple to share their experiences with others who have faced similar situations (Honea-Fleming, 1986; March, 1986; Andrews et al.,

1992; McNaughton-Cassill et al., 2000). As an extension of the research examining the effect of stress on ART treatment outcomes, researchers have begun to examine the efficacy of psychoeducational interventions as well as benefits to patients in terms of success rates with ART treatment (Domar et al., 2000; McNaughton-Cassill et al., 2000).

As with much of the research that has been conducted to date relating to stress and infertility, these recent studies have been criticized for various limitations. One limitation cited is the use of convenience samples and/or small sample sizes. In addition, much of the research on this topic is based on nonexperimental designs. Several statistical models using combinations of biomedical factors in relation with in vitro fertilization outcomes demonstrate limited external validity because they are based only on stable variables. Additionally, in the area of infertility, even well designed, randomized, controlled trials rarely have sufficient statistical power to demonstrate small but clinically significant differences between control and treatment groups (Hughes, 1992; Smeenk et al., 2001; Wilson & Kopitzke, 2002).

Stress and infertility can be viewed as dynamic and circular. Studies investigating the role of stress on infertility treatment outcomes have led to conflicting results. Several methodological issues may have contributed to these varying results including small sample size, insufficient amount of power to detect small but significant differences, and homogenous groups of women in terms of ethnicity, age, and socio-economic status included in the samples. This study will use the accumulated evidence regarding the role of stress and the efficacy of

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patient education programs through psychoeducational interventions on infertility treatment outcomes through a meta-analysis.

Meta-Analysis in Medical Research

Gene Glass first used the term "meta-analysis" in 1976 to refer to a philosophy, not a statistical technique. Glass argued that a review of the literature should be as systematic as primary research and should interpret the results of individual studies in the context of the findings. Over the past three decades, meta-analysis has grown from an unheralded preoccupation of a very small group of statisticians working on problems of research integration in education and psychotherapy to an academic industry encompassing an assortment of procedures used in a variety of disciplines. Its popularity in the social sciences and education pales in comparison to its influence in medical research. Evidence-based medicine has been given increasingly more emphasis in recent years. Evidence-based medicine focuses on the examination of empirical evidence from clinical research for sound medical decision-making. Meta-analysis provides a quantitative approach to the review of the medical literature and is especially useful in providing information regarding the strength and quality of the evidence either supporting or refuting a medical practice as well as providing empirical evidence for developing practice guidelines. In medical research, meta-analysis uses the accumulated evidence about a treatment or procedure to provide guidance to clinicians and to suggest directions for future study. The use of meta-analysis has generated considerable interest in the medical literature and has proven to be a powerful tool in the field

of perinatology. Likewise, obstetrics is one field leading other medical specialties in the attempt to systematically review all randomized trials conducted in its discipline (Hughes, 1992; Peipert & Bracken, 1997).

There are several advantages to conducting a meta-analysis. First, it allows the researcher to identify gaps, problems and limitations in the primary research base. Many individual trials and observational studies lack sufficient statistical power to detect small but clinically significant differences. One advantage of a meta-analysis is its ability to increase statistical power to detect overall differences between groups and within subgroups. In addition, this technique allows researchers to resolve some uncertainty and controversy when individual research studies provide opposing conclusions. Through increasing sample size, meta-analysis can provide stronger evidence for or against a treatment effect than one can derive from any of the individual studies because a more precise estimate of the effect size or measure of association is generated. In addition, meta-analysis allows researchers to investigate research questions not posed at the start of an individual treatment trial. Finally, another major advantage of this type of research review is the opportunity for others to judge the quality of its conclusions (Hughes, 1992; Peipert & Bracken, 1997).

Problem Statement

The psychological impacts of infertility have been well documented in the literature. While research findings regarding the prevalence of distress and depressive symptoms in infertile women are inconsistent, there is evidence to support that at least some women who confront infertility are at risk for

heightened distress and depressive symptoms. Psychoeducational interventions may provide an important component to the treatment of infertility. In addition, these programs may prove to be an effective intervention in preventing the anticipated increase in psychological distress as the duration of infertility increases. While several theoretical models postulate the effects of stress on infertility and infertility treatment outcomes as well as the efficacy of psychoeducational interventions, a synthesis of the accumulated data incorporating a qualitative assessment of the methodology of reviewed studies as well as a quantitative method of combining and analyzing the data examining the effects of stress on ART treatment outcomes is nonexistent.

<div align="center">Research Purpose and Questions</div>

Although sometimes viewed as a social condition of childlessness, infertility is a significant health problem. The role of stress on infertility and treatment outcomes is complex, often leading researchers to conflicting conclusions. The purpose of this study is to investigate the impact of stress on the success of Assisted Reproductive Technology (ART) treatments and to determine whether psychoeducational interventions mitigate the impact of stress during Assisted Reproductive Technology (ART) treatments. The study will test two hypotheses.

1. Increased levels of stress will reduce the likelihood of Assisted Reproductive Technology (ART) treatment success, and

2. Psychoeducational interventions provided to patients receiving infertility treatment will mitigate the effects of stress during Assisted Reproductive Technology (ART) treatment.

Limitations of the Study

Limitations to any meta-analysis include methodological variability and bias. With respect to methodological variability, the extraction and pooling of data brings about statistical concerns of heterogeneity relating to the problem of variability among studies and the appropriateness of combining them into one meta-analysis (Hughes, 1992; Peipert & Bracken, 1997).

The possibility for bias in a meta-analysis exists in several forms. First, the potential for publication bias, that is, a bias toward published studies that have demonstrated "positive" results, remains a concern with all meta-analytic studies. The omission of negative data, which may arise more frequently with unpublished trial studies, could lead to erroneously enhanced treatment effects and outcomes. Conversely, the inclusion of unpublished studies may lead to the inclusion of studies of poorer quality since they have not passed a peer review process. In addition to publication bias is the potential for selection bias, which may occur when the researcher is selecting studies for inclusion in the meta-analysis. A researcher conducting a meta-analysis may unwittingly be partial to the selection of certain studies over others for inclusion in the analysis. Once the studies have been selected, the potential for bias in the quality assessment of these studies also exists (Hughes, 1992; Peipert & Bracken, 1997).

Professional Significance of the Study

The relationship between stress and infertility has long been an issue of interest and debate among researchers and physicians. Several aspects of the relationship between stress and infertility or infertility treatment outcomes have been examined by researchers through independent trial studies. Recognizing the emotional aspects of infertility, many physicians treating couples for infertility now also offer their patients psychoeducational interventions. Over recent years, investigation into the effects of stress on ART treatment outcomes has expanded. An extension of this research includes studies focusing on the mitigating effects that psychoeducational interventions have on elevated stress levels experienced by couples during ART. However, results of these studies are conflicting, leading to a muddled picture of the relationship between stress and treatment outcomes and the mitigating impact of these psychoeducational interventions. This study will combine the results of many studies, providing a comprehensive synthesis of existing research on the topic of the effects of stress on ART treatment outcomes and the impact of psychoeducational interventions on ART treatment outcomes. To date, this is the only synthesis of current studies delineating the role of stress on ART treatment outcomes and the efficacy of psychoeducational interventions provided to infertility patients experiencing stress. This study has the potential to resolve uncertainty and controversy that exists with respect to this topic in the literature and to provide physicians and others with evidence-based research to guide their treatment practices with infertile couples.

Definitions of Terms

Anxiety. An ambiguous emotional reaction of a culmination of fear resulting from a threat to an individual's well-being in which the individual does not know what is going to happen, when it is going to happen, and therefore, does not know what is to be done about it.

Artificial Insemination (AI). The injection of semen into the vagina by means of a syringe rather than by coitus.

Assisted Reproduction Technology (ART). Any fertility procedure in which both oocytes and sperm are handled outside the body.

Asthenospermia. Poor motility or movement of the sperm in a man's ejaculate.

Azoospermia. The complete absence of sperm in a man's ejaculate.

Congenital. A condition present at birth.

Contraceptively Sterile. Represents women who underwent tubal operations or women married to men who underwent vasectomies and other sterilizing operations in order to prevent pregnancy.

Distress. Thought of as "bad stress" which is an inherently unpleasant emotional experience such as frustration and resentment associated with unpleasant outcomes and destructive to health.

Effect Size. Displays the magnitude of effects in terms of standard deviation units and allows comparison across different clients or studies and is calculated as the difference between the means of 2 groups divided by the standard deviation of the control group.

Embryo. Fertilized ovum and sperm that have begun cellular division.

Endocrinology. The branch of biology dealing with the endocrine glands and their secretions especially in their relation to their processes or functions.

Epidemic. A rapid spread or increase in the occurrence and prevalence of a condition or disease.

Etiology. The cause or origin of a disease or condition.

Fertility. The ability for a man and a woman to reproduce.

Fecund. Producing or capable of producing children.

Fecundability. The monthly probability of conception without the use of contraception.

Follicle. One of the small ovarian sacs containing an immature ovum.

Follicular Phase. A stage in the menstrual cycle that begins with the onset of menstruation and ends with ovulation.

Gamete. Raw ovum and sperm.

Gamete Intrafallopian Transfer (GIFT). A specialized technique by which a woman's mature oocyte and her partner's washed sperm are mixed together in a syringe and inserted via laparoscopy into the woman's fallopian tube.

Idiopathic Infertility. Infertility of unexplained etiology.

Impaired Fecundity. Any woman of childbearing age who reported whether it is difficult, impossible, or dangerous to become pregnant or carry a pregnancy to term.

Intracytoplasmic Sperm Injection (ICSI). A form of micromanipulation involving the injection of a single sperm directly into the cytoplasm of a mature oocyte

using a glass needle (pipette), with the resulting embryo later implanted in the uterus for gestation.

Intrauterine Insemination (IUI). The injection of semen into the uterine by means of a syringe and catheter rather than by coitus.

In Vitro Fertilization (IVF). A specialized technique by which an ovum is fertilized by sperm outside of the body, with the resulting embryo later implanted in the uterus for gestation.

Infecund. Sterility; when the fecundability of a couple is zero.

Infertility. The state in which a couple desiring to have a child cannot conceive after 12 months of unprotected intercourse.

Luteal Phase. Usually referred to as "days past ovulation" (DPO) and refers to the part of a woman's menstrual cycle that begins at ovulation and ends the day before menstruation.

Meta-Analysis. A statistical process of combining the results of many quantitative studies for an overall synthesis.

Neuroendocrinology. The study of the anatomical and physiological interactions between the nervous and endocrine system.

Noncontraceptively Sterile. Represents those women who had surgery to correct medical problems with their reproductive organs, such as hysterectomies for fibroid tumors or endometriosis.

Oligospermia. Low concentrations of sperm present in a man's ejaculate.

Oocyte. An immature egg cell contained in the follicle.

Parity. The condition or fact of having born offspring.

Primary Infertility. Women who have never achieved pregnancy.

Psychoeducational Interventions. Any therapeutic technique, which includes educational training, aimed at the reduction of distress experienced by patients participating in medical treatment.

Secondary Infertility. Women who have achieved pregnancy at least once before, regardless of the outcome, and who cannot achieve a subsequent pregnancy.

Sterility. The absolute inability to reproduce.

Stress. A response to any noxious agent in an individual's environment. Three conceptualizations of stress include the response-oriented approach, the stimulus-oriented approach, and the interaction approach.

Stressors. External events or conditions affecting an organism.

Subfecund. Infertile.

Teratospermia. An increased percentage of abnormally shaped sperm in a man's ejaculate.

Zygote. Fertilized ovum and sperm prior to cellular division.

Zygote Intrafallopian Transfer (ZIFT). A specialized technique by which a woman's mature oocyte is fertilized by her partner's washed sperm outside of the body, with the resulting zygote being inserted via laparoscopy into the woman's fallopian tube.

CHAPTER TWO: LITERATURE REVIEW

Introduction

Much public attention has been given to infertility and infertility treatment, leading many to believe that infertility has become an epidemic. While estimates of infertility and trends demonstrating an increase in number of couples seeking treatment for infertility have risen over the years, the evidence does not support the claims that infertility has become an epidemic. However, the incidence rate of infertility does support the conclusion that infertility is an important societal health issue. Therefore, infertility treatment and research in this field are important to the further advancement of this specialized field.

One longstanding popular topic in the field of infertility has been the relationship between stress and infertility. Shaped by cultural, social, and personal expectations, infertility can create overwhelming stress. Research literature provides a plethora of information documenting the psychological impacts of infertility. While early investigations focused on attributing idiopathic infertility to psychological maladjustment, current research focuses largely on the impact of stress on ART treatment outcomes. In addition, investigations into the efficacy of psychoeducational interventions and their impact on the effects of stress on ART treatment outcomes have begun. However, investigations into the relationship between stress and infertility vary considerably, leading many to conflicting conclusions. One source of the controversies may lie in the ambiguity

of the definition of stress. Since the beginnings of stress research, a variety of theoretical conceptualizations of stress have evolved leading to a multitude of definitions and measures of stress. In addition, many researchers use the terms "stress" and "anxiety" interchangeably, leading to an even more unclear definition of stress. Three classical conceptualizations of stress include the response-oriented approach, the stimulus-oriented approach, and the interaction approach. While stress is conceptualized in broad, ambiguous terms to include any noxious agent in an individual's environment, anxiety is regarded by many researchers and theorists as an emotional reaction to a perceived threat to an individual's well being and may represent only one of many emotional responses to a stressful situation or event. Although investigations into the relationship between stress and infertility span a multitude of topics, a common theme examined is the distress experienced by individuals and couples seeking infertility treatment. To understand the complex and often ambiguous relationships between stress and infertility, one needs to grasp the scope of the issues surrounding infertility as well as the prevalence of infertility, the conceptualizations and theoretical approaches to stress, and evidence of the relationships between stress and infertility provided through research.

The Infertility Problem

Definition, Prevalence and Trends of Infertility in the United States

Fertility is the ability for a man and a woman to reproduce. The epidemiological term, fecundability, refers to the monthly probability of conception without the use of any contraception (Jansen, 1993; Speroff, et al,

1994; Tsaltas, 1997). A couple is said to be subfecund, or infertile, when there is

an involuntarily long interval until their first conception or between births. A

common definition of infertility is the state in which a couple desiring to have a

child cannot conceive after 12 months of unprotected intercourse (Tsaltas, 1997).

Failure to conceive after 12 months of unprotected intercourse is taken to be

abnormal as 90% of couples will have conceived within that time (Tietze, 1956,

1968; Tsaltas, 1997).

Broadly defined, infertility is a disease of the reproductive system that

impairs conception and the ability to carry a pregnancy to full term leading to live

birth (ASRM, 2000-2003; National Women's Health Information Center [NWHIC],

2003). Infertility is either classified as primary or secondary. Primary infertility

refers to women who have never achieved pregnancy, whereas, secondary

infertility refers to those women who have achieved pregnancy at least once

before, regardless of the outcome, and who cannot achieve a subsequent

pregnancy (Thonneau et al., 1991; Seibel, 1993; Tsaltas, 1997). Sterility, on the

other hand, is the absolute inability to reproduce. When the fecundability of a

couple is zero, for whatever reason, the couple is defined as infecund, or sterile

(Jansen, 1993; Seibel 1993; Tsaltas, 1997). Although the true incident rate of

sterility is unknown, it is believed that 3-5% of the population is sterile (Spira,

1986; Jansen, 1993, Tsaltas, 1997).

The incidence rate of infertility in less industrialized nations is markedly

higher and reflects a greater proportion of infertility problems attributed to

infectious diseases than those in the United States and other industrialized

nations. Over recent years, a number of factors have contributed to the public's perception that there is an infertility epidemic in the United States. This perception could be tied to the "medicalization" of infertility and treatment. Medical advancements in the understanding of human endocrinology and medical technology have significantly impacted the development of this specialized field. New medications and technologies have been noteworthy advancements offering childless couples hope to conceive. Also, the supply of physicians trained to provide specialized infertility services to couples has dramatically increased over the past 20 years. In addition to these medical and technological advancements, several social factors have influenced the development of the medical industry in infertility. The first factor includes the sexual revolution and the increased incidence of sexually transmitted diseases. Secondly, there is an increase in women entering the job market and delaying childbearing until ages when it is considerably more difficult to conceive. In addition, the aging of baby boomers has increased the absolute numbers of couples trying to have children. Finally, in addition to the increased number of women trying to conceive and the increase in the number of women delaying trying to conceive until they are older, the number of healthy infants, especially white infants, available for adoption has decreased. The development of infertility diagnosis and treatment as a medical industry along with intense media attention given to couples seeking help from physicians for infertility has provoked the perception that infertility has become an epidemic (Mosher & Pratt, 1991; Whitford & Gonzalez, 1995; Chandra, 2003).

Estimates regarding the actual incidence of infertility, primary and

secondary, vary greatly, ranging from 8% to 33%, depending on the criteria used

to define infertility and the population included (Seibel, 1993; Schneider, 2000).

The National Survey of Family Growth (NSFG) and its predecessor surveys, the

Growth of America Study in 1955 and 1960 and the National Fertility Survey in

1965 and 1970, have been the only source providing reliable national estimates

regarding the actual incidence of infertility, both primary and secondary, in the

United States. To date, five NSFGs have been conducted by the National Center

for Health Statistics – 1973, 1976, 1982, 1988, and 1995. The primary purpose

of the 1973-1995 surveys was to provide reliable national data on marriage,

divorce, contraception, infertility, and the health of women and infants in the

United States as well as to provide information on factors that affect the nation's

birth rate. The last NSFG survey, conducted in 1995 by the NCHS, contained an

enhanced set of infertility questions that covered the respondent's pregnancy

history, past and current use of contraception, the ability to bear children, the use

of medical services for family planning, infertility, prenatal care, marital history,

and associated cohabiting unions. The Survey Research Center of the

University of Michigan is presently working on the 2002 NSFG survey and the

findings are projected to be released in early 2004. The 2002 NSFG includes

interviews and free-response items online with both men and women. Survey

participants are being asked questions regarding their schooling, work, marriage

and divorce, contraceptive use, infertility, parenting, and related medical care.

The 2002 NSFG is distinguished from previous studies in that it captures, for the

first time, reliable data for men, providing essential information regarding national infertility prevalence (NCHS, 2001; Chandra, 2003).

The NSFG produces data that classifies women or couples into three major groups: surgically sterile, impaired fecundity, or fecund. In addition to these broad categories, measures of infertility are included. The category for surgically sterile is reported as either "contraceptively sterile" or "noncontraceptively sterile". The sub-category of contraceptively sterile represents women who underwent tubal operations or women married to men who underwent vasectomies or other sterilizing operations in order to prevent pregnancy. Noncontraceptively sterile represents those women who had surgery to correct medical problems with their reproductive organs, such as hysterectomies for fibroid tumors or endometriosis. Impaired fecundity included any woman of childbearing age who reported that it is difficult, impossible, or dangerous to become pregnant or carry a pregnancy to term. Impaired fecundity includes all women regardless of marital status. Infertility status in the NSFG refers to married couples of childbearing age that have not been surgically sterilized, have not used contraception, and have not become pregnant for at least 12 months. For unmarried women, impaired fecundity refers only to the woman herself whereas, for married women, the questions capture information about female and male infertility or impaired fecundity (Chandra, 2003; Mosher & Pratt, 1991).

The most recent report of NSFG findings from the 1995 administration estimated that 7.1% of married couples, or 2.1 million, in which wives were aged

15 to 44 years were infertile. Among all women of reproductive age, 24% were

surgically sterile. An additional 10.2% (6.1 million) had impaired fecundity (CDC,

1997). The ratio of patients presenting with primary and secondary infertility

represents 67% to 71% of patients categorized as presenting primary infertility

and 29% to 33% presenting with secondary infertility (Hull et al., 1985; Thonneau

et al., 1991; Tsaltas, 1997; Templeton et al., 1999).

Table 1 below presents historical findings from the NSFG regarding the

fertility of women of childbearing age. As shown in Table 1, in 1995, 24 percent

of all women ages 15-44 (or their husbands, if they were married) were

contraceptively sterile, including the three percent of women with no children and

40 percent of women with one birth or more, reflecting an increase when

compared to 1982. Another seven percent of women had been surgically

sterilized for noncontraceptive reasons, including one percent of women with no

children and 11 percent of women with one birth or more, reflecting a decrease in

the percentage of women as compared to 1982. In addition, approximately 6.1

million women (or 10.2 percent) had impaired fecundity reflecting an increase

when compared to 1982. Of the 6.1 million women with impaired fecundity, 2.8

million had no children and 3.3 million had one or more children, reflecting an

increase since 1982 with 1.9 million and 2.6 million, respectively (Mosher & Pratt,

1990; CDC, 1997; Chandra, 2003).

Table 1

Percent distribution of women 15-44 years of age by fecundity status, according to parity and age: United States, 1982 to 1995.

Age in Years	Surgically Sterile						Impaired Fecundity			Fecund		
	Contraceptive			*Noncontraceptive*								
	1982	*1988*	*1995*	*1982*	*1988*	*1995*	*1982*	*1988*	*1995*	*1982*	*1988*	*1995*
Parity = 0												
15-44	1.7	2.8	2.8	1.4	1.5	1.5	8.4	8.8	11.0	88.5	86.9	84.7
15-24	0.1	0.2	0.2	0.0	0.0	0.1	4.1	4.1	5.5	95.8	95.7	94.3
25-34	3.3	3.1	2.9	1.8	1.6	0.7	14.7	13.4	13.9	80.2	82.0	82.5
35-44	10.3	15.8	11.9	12.7	9.2	8.1	25.7	21.4	25.7	51.3	53.6	54.3
Parity = 1 or More												
15-44	31.2	39.0	39.7	10.5	7.1	4.2	8.5	8.1	9.6	49.9	45.8	46.5
15-24	9.0	9.8	6.7	0.6	0.7	0.3	5.2	7.7	8.4	85.2	81.8	84.6
25-34	28.1	32.8	32.1	6.1	3.3	1.5	8.1	7.8	9.8	57.8	56.1	56.7
35-44	42.7	52.3	52.9	19.0	12.5	7.2	10.1	8.5	9.8	28.1	26.7	30.1
Parity = All												
15-44	18.6	23.3	24.2	6.6	4.7	3.1	8.4	8.4	10.2	66.3	63.6	62.5
15-24	2.1	2.0	1.6	0.2	0.2	0.1	4.3	4.8	6.1	93.4	93.0	92.2
25-34	21.0	22.9	22.0	4.9	2.7	1.2	10.0	9.6	11.2	64.2	64.7	65.6
35-44	38.7	46.3	45.3	18.3	12.0	7.4	12.1	10.6	12.8	31.0	31.0	34.6

Note. Parity is defined as the number of children born.

Adapted from "Fertility, Family Planning, and Women's Health: New Data from the 1995 National Survey of Family Growth", by Centers for Disease Control and Prevention, 1997, p. 59; "Fecundicity and Infertility in the United States, 1965 – 88", by William D. Mosher & William F. Pratt, *Advanced Data,* 192, December 4, 1990, p. 4.

Although the percent of women with impaired fecundity increased 1.8 percentage points, from 8.4 percent in 1982 and 1995 to 10.2 percent in 1995, no evidence supports the perception that infertility has become an "epidemic". Further analyses investigating a variety of potential reasons explaining these findings are needed. One plausible explanation is that the changes observed since 1982 are merely an artifact of the aging baby boom generation. Other

plausible explanations of this trend include: women are waiting longer to begin

trying to start their families; the 1.6 percentage point drop in the percent

categorized as surgically sterile for noncontraceptive reasons; the many new

medications and treatments now available to couples; as well as an increase in

the number of physicians specializing in this field and couples seeking advice

and treatment (Mosher & Pratt, 1991; CDC 1997; Chandra, 2003).

While earlier studies have projected the number of women in the United

States with impaired fecundity to range from 5.1 million in 1995 to 4.8 – 5.9

million in 2020, a more recent study has provided projection data while

considering several trends evidenced in the 1995 NSFG. Given population

projections provided by the U.S. Bureau of the Census for the years 2000 to

2025, Stephen and Chandra (1998) estimate that nearly 6.5 million women can

be expected to be infertile in the year 2025. While this estimate cannot possibly

anticipate factors such as the emergence of highly prevalent new disease

processes related to infectious agents, environmental chemicals, or other

unpredictable events, it highlights the importance of continuing research in this

field (Stephen, 1996; Phipps, 1996; Stephen & Chandra, 1998; Schneider, 2000).

Physical Causes of Infertility

The diagnosis and treatment of infertility contrasts with almost all other

medical conditions in that it involves a couple. When a couple presents concerns

of infertility to their physician, thorough assessment of both individuals is

essential. Approximately 40 percent of the causes of explained infertility can be

established as male factors such as abnormal spermatogenesis, abnormal

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motility of the spermatozoa, anatomic disorders, endocrine disorders, and sexual

dysfunction. Female factors such as cervical, uterine or tubal, ovulatory,

peritoneal and pelvic disorders account for approximately another 40 percent of

explained infertility cases. In approximately 20 percent of the cases, explained

infertility problems can be attributed to a combination of both male and female

factors. In addition to attributing infertility to female, male, or a combination of

both female and male factors, the etiology of infertility is sometimes defined as

unexplained infertility. Estimates regarding the prevalence of idiopathic infertility

vary considerably due to a number of reasons. The proportion of cases of

infertility that are unexplained range from 0 to 31 percent. Most studies between

1950 and 1995 found an average rate between 15 and 25 percent.

Approximately 2 to 15 percent of infertility cases are categorized as unexplained

or idiopathic infertility where no diagnosis can be made following a thorough

investigation (Seibel, 1993; Schneider, 2000).

Conception is an intricate and complex neuroendocrinologic process. Any

one of a number of physical factors may interfere in this process and contribute

to infertility. Approximately 30 to 40 percent of infertility problems among women

are due to peritoneal factors. The two most common peritoneal factors are

endometriosis and tubal disease. Failure to ovulate is the major problem in

approximately 25% (Seibel, 1993) of infertility diagnoses. Although ovulation

may be affected by several sources, the three most common causes are extreme

emotional distress, excessive weight loss or gain, and excessive exercise.

Cervical factors are identified in no more than 5 to 10% (Seibel, 1993) of infertility

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cases; these disorders may be either congenital or acquired. Regardless of their etiology, these disorders can significantly impact the process of conception through both the receptivity of the cervical mucus and the ability of sperm to reach and survive in the mucus. Approximately 5% (Seibel, 1993) of infertility cases are caused by uterine factors. Uterine factors are commonly structural abnormalities and are associated with fetal wastage and increased frequency of obstetric problems (Seibel, 1993, 1997; Pernoll, 2001; Schneider, 2000).

Factors contributing to infertility among men can be attributed to several types of disorders. Abnormal spermatogenesis, including low semen volume, high sperm viscosity, and low sperm motility may occur as the result of mumps orchitis during childhood, chromosomal abnormalities, cryptorchidism, chemical or radiation exposure, variocele, testicular failure, obstruction, or other anatomical disorders. In addition, endocrine disorders may also contribute to male-factor infertility (Seibel, 1993; Schneider, 2000; Pernoll, 2001).

Before 1900, virtually all cases of infertility were classified as unexplained due to the lack of clinical tests available to diagnose the etiology. Although innovations between 1900 and 1940 have led to considerable improvement in the diagnosis of tubal, seminal, and ovulatory problems, the etiology of all cases of infertility cannot be diagnosed. Infertility is categorized as unexplained or idiopathic when an extremely long delay in conception occurs by chance in otherwise healthy couples or because underlying defects cannot be detected with current clinical diagnostic tests or tools. Also contributing to idiopathic infertility is the declining fertility of older female partners. It is important to recognize that in

any normal population, otherwise healthy couples may appear to be infertile by chance alone because a small proportion of healthy couples have low fecundity, and therefore may not conceive within a year (Seibel, 1993; Collins, 1997; Schneider, 2000). A recent study conducted by David Dunson suggests that among outwardly healthy couples with no known conditions associated with infertility who failed to conceive naturally within the first year, most will conceive naturally in the second year. Dunson reported that 97% of women ages 19 to 26, 94% of women ages 27 to 34 years, and 91% of women ages 35 to 39 years conceived naturally within the second year, provided that the male partner was under the age of 40. If the male partner was over the age of 40, only 84% of women ages 35 to 39 years conceived naturally within the second year. Therefore, Dunson asserts that couples who might otherwise be categorized with idiopathic infertility should be patient and that physicians should not intervene too quickly with assisted reproductive techniques unless there are known reasons for a couple not conceiving naturally within a year (Hawkins, 2002).

In addition to identified physical causes of infertility, other demographic factors contributing to impaired fecundity include advancing age and smoking. The decline of fecundity among married couples with advancing age has been documented throughout the research literature. Approximately one-third of women who defer pregnancy until their mid to late 30s will have an infertility problem. At least half of the women waiting to conceive until over the age of 40 will have an infertility problem. Although the risk of infertility related to increasing age has primarily been focused on women, the changes in male fertility with

aging, although modest, are significant. Advancing age in men is significant for two major reasons. First, the quality of sperm decreases with age and is evidenced by the absolute frequency of autosomal dominant disease representing 0.3% to 0.5% among offspring in fathers 40 years of age and older (Seibel, 1993). In addition, men with advancing age also demonstrate diminished fecundity, evidenced through the rates of conception. The rate at which men over the age of 40 impregnate their partner within 6 months is one-third (Seibel, 1993) of that of men under the age of 25 which may be due to factors such as involution of testicular function, decreased sperm production, and maturation arrest of spermatogenesis, all of which have been associated with advancing age (Collins & Rowe, 1989; Seibel, 1993; Speroff et al., 1994).

Another contributing factor to decreased fecundity is smoking. While the hazardous effects of smoking on reproduction have been widely discussed, epidemiological studies have documented that fecundity decreases directly with the number of cigarettes smoked. Fecundity decreases 25% (Seibel, 1993) in women who smoke up to 20 cigarettes per day in comparison to nonsmokers. Among those women who smoke more than 20 cigarettes a day, women demonstrate a 57% (Seibel, 1993) decrease in fecundity in comparison to nonsmokers. In addition, ectopic gestations are far more frequent among smokers than among nonsmokers. Among men, cigarette smoking reduces sperm density by 22% on average. While results of studies examining the effects of smoking on human sperm morphology and motility are inconsistent, adverse byproducts of smoking are evidenced in men through testicular atrophy, blocking

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spermatogenesis, and in experimental animals through altering sperm morphology. In addition to these effects, male smokers who have a testicular varicocele are 10 times more likely to have oligospermia than nonsmokers who do not have a varicocele. Based on this evidence, couples with unexplained infertility or in whom fertility is marginal, cessation of smoking may play a substantive role in increasing fecundity (Baird & Wilcox, 1985; Howe et al., 1985;; Phipps et al., 1987; Seibel, 1993).

Physical Infertility Treatment Options

Since the 1950s, the treatment of infertility has evolved dramatically. During the 1960s, safe and effective ovulation-inducing medications were developed and introduced. Refinements in surgical techniques and technology during the 1970s paved the way for the development of microsurgery for tubal disease. Further developments in cell culture and embryology during the 1980s produced in vitro fertilization and related assisted reproductive technologies. Finally, during the 1990s, the treatment of infertility was further refined to include micromanipulation of cells through the development of intracytoplasmic sperm injection (ICSI) and other procedures (Seibel, 1993; ASRM, 2001). It appears that with advancing technology and an increased number of specialists in the field, the diagnosis and treatment of infertility will progress to a sub-cellular level and molecular biology will move to the forefront.

Hormonal Treatment

Two primary fertility hormones control follicle development and ovulation in women and sperm development in men. If the body does not produce these

hormones in exactly the right way, a hormone imbalance or deficiency may cause infertility. In women, treatment with gonadotropins can increase the likelihood of conception by stimulating inactive ovaries to ovulate or to produce more than one egg at a time. In men, gonadotropins can stimulate the production of sperm. However, fewer than 5 percent of infertile men have a hormonal disorder that can be treated with hormonal therapy (Seibel, 1993, 1997; Speroff et al., 1994; Lunenfeld et al., 1997; Pernoll, 2001).

By far, the most prevalent medication for ovulation induction is clomiphene citrate. Clomiphene citrate stimulates ovulation for women with irregular menstrual cycles or stimulates the development of multiple eggs during a woman's menstrual cycle. Clomiphene citrate is an anti-estrogen that acts on the brain to stimulate the ovaries. It is an oral medication taken during the early part of a woman's menstrual cycle which blocks estrogen receptors in the hypothalamus, causing the hypothalamus to signal the pituitary gland to release more follicle stimulating hormone (FSH) and luteinizing hormone (LH) into the bloodstream. These increased levels of FSH lead to the development of the follicle and egg, which, in turn, secretes more estrogen into the bloodstream. Approximately one week after ingestion of the last clomiphene citrate tablet, the hypothalamus receptors are no longer blocked, triggering an LH surge in response to the artificially elevated levels of estrogen in the bloodstream. At the proper dosage level, ovulation usually occurs 7 to 10 days after the last tablet is ingested. Serious side effects associated with this medication are rare. Multiple births, the most of which are twins, occur in less than 10% of the cases. Other

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side effects, including but not limited to hot flashes, breast tenderness, mood swings, visual and gastrointestinal symptoms, are not uncommon and completely reversible upon cessation of the medication.   A rather large percentage of couples report that the use of clomiphene citrate results in some emotional side effects. The emotional instability often experienced by patients using clomiphene citrate is described by one patient:

> "Hormone hell is probably the best way to describe it. By third or fourth day of taking it, I would become hysterical for absolutely no reason. I felt as if I had no control over my body. I began to wonder if this was worth it. But, it only lasted a few days, and we all got through it. But it wasn't fun" (Seibel, 1993, 1997; Speroff et al., 1994; Chamoun et al., 1997; Pernoll, 2001).

In addition to clomiphene citrate, two main types of medications are used to induce ovulation: Gonadotropins containing follicle stimulating hormones (FSH) and Human Menopausal Gonadotropins (hMG). When given to premenopausal women, these medications stimulate the ovaries to form follicles that mature and produce eggs. In clinical use for 30 years, Human Menopausal Gonadotropin (hMG) is distributed as a lyophilized powder containing a luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones stimulate the woman's ovaries to produce more follicles, thus increasing the number of eggs available for fertilization. The FSH is primarily responsible for follicular recruitment, selection, growth, and ripening of a woman's eggs. The LH part is

responsible for the final maturation of the FSH-stimulated follicles, ovulation, and

transformation of the follicular remnants into functional corpora lutea. Unlike

clomiphene citrate treatment, gonadotropins act directly on the ovaries and are

often prescribed to stimulate the development of multiple eggs. Gonadotropin

treatment requires a series of injections and careful monitoring of follicular

development through trans-vaginal ultrasound and serum estradiol levels

throughout the cycle. If satisfactory blood estradiol levels and follicle

development occur, ovulation is then induced with an intramuscular (IM) injection

of human chorionic gonadotropin (hCG). In less than 2% of the cases, severe

overstimulation occurs and the cycle must be cancelled. Multiple pregnancies

occur in approximately 26 to 40% of cycles, 75% of which are twins while 25% is

triplets or more. The most common reason for using hMG is anovulation.

However, it is also used to treat cases of infertility caused by oligoovulation,

luteal phase deficiency, idiopathic infertility, and in the harvesting of multiple

follicles for in vitro fertilization, gamete intrafallopian transfer, zygote intrafallopian

transfer, and intracyplasmic sperm injection (Seibel, 1993, 1997; Speroff et al.,

1994; Pernoll, 2001).

Follicle Stimulating Hormone (FSH) became available for clinical use in

the United States in 1986. FSH is a further purification of hMG and is primarily

indicated to treat clomiphene-resistant patients with polycystic ovary disease

(POCS). As with the hMG, FSH stimulates the ovaries to produce more follicles,

thus increasing the number of eggs. These medications are initiated between

days 4 and 6 of a woman's menstrual cycle and are administered with a

subcutaneous (SQ) injection. Ovulation may occur spontaneously but is much more consistent if human chorionic gonadotropin (hCG) is administered. As with hMG, ovulation induction with FSH must be carefully monitored through measurements of serum estradiol levels and follicular development through pelvic ultrasound to reduce the potential for ovarian overstimulation and multiple births (Seibel, 1993, 1997; Speroff et al., 1994; Pernoll, 2001).

Gonadotropin-Releasing Hormone (GnRH) is responsible for the release of LH and FSH from the pituitary gland. GnRH regulates the reproductive cycle in both sexes. Pulsatile secretion of GnRH from the hypothalamus is key in establishing normal gonadal function. Failure of this release results in isolated GnRH deficiency that can be distinguished by partial or complete lack of GnRH-induced LH pulse, normalization with GnRH replacement, and otherwise normal hypothalamic-pituitary neuroanatomy and neurophysiology. This medication can be administered subcutaneously or intravenously. Side effects of this medication include ovarian overstimulation, multiple births, infection at the indwelling catheter site, allergic reactions, and rarely anaphylaxis with the development of anti-GnRH antibodies (Seibel, 1993, 1997; Speroff et al., 1994; Pernoll, 2001).

GnRH agonists are prescribed for nearly all patients during gonadotropin therapy for IVF or GIFT to prevent premature ovulation. Administration of GnRH agonists can be started either in the luteal phase around day 21 of a woman's menstrual cycle or in the early follicular phase just after the menstrual period has begun. GnRH agonists such as Lupron and Synarel are synthetic imitators of GnRH. However, when treated with GnRH, the pituitary initially increases its

production of FSH and LH, but then stops FSH and LH production due to "down regulation". Therefore, GnRH agonists serve to suppress the ovaries and provide the physician with greater control over controlled ovarian hyper-stimulation and in preventing premature ovulation (Seibel, 1993, 1997; Speroff et al., 1994; Pernoll, 2001).

Prolactin is a hormone produced by the pituitary gland and is usually elevated in women during pregnancy and breast-feeding to promote lactation. When prolactin is elevated in non-pregnant and non-lactating women, the result can be irregular menstrual cycles or an inadequate luteal phase. Bromocriptine is a medication designed to lower the levels of prolactin in the bloodstream. Bromocriptine is prescribed in cases of elevated prolactin levels and results in 85 to 90% ovulatory success rates when other infertility factors are not present (Seibel, 1993, 1997; Speroff et al., 1994; Pernoll, 2001).

Another hormonal imbalance that is present in a few women is characterized by excess of amounts of androgens, or male type hormones. These increased levels of androgens, such as testosterone and androstenedione, may interfere with processes such as normal follicular development and ovulation. In these cases, low doses of corticosteroids are used to lower the androgen levels to within normal range (Seibel, 1993, 1997; Speroff et al., 1994; Pernoll, 2001).

Surgical Treatment

Advancement in surgical technique is one the many developments in reproductive endocrinology over the past several decades. Magnification and

microsurgery have significantly contributed to the advancements made in infertility surgery. Advancements in magnification include loupes and later operating microscopes while microsurgery has been advanced through developing technologies such as intricate surgical tools and techniques (Seibel, 1993). For women, surgical options are available for diagnostic as well as therapeutic treatment. For diagnostic purposes, the hysterosalpingogram (HSG), laparoscopy, and hysteroscopy are common procedures. These procedures are useful diagnostic procedures for identifying tubal disease and obstruction, and conditions such as endometriosis and fibroid tumors that may interfere with a woman's ability to achieve a successful pregnancy. Any pelvic conditions that may inhibit a woman's ability to conceive may also be corrected at the time the laparoscopy and hysteroscopy are performed (Seibel, 1993, 1997; Speroff et al., 1994; Pernoll, 2001).

Among men, surgical techniques are performed for conditions such as varicocele or to remove any obstruction in the sperms' path. Blockages can be found in the vas deferens, epididymis, or in the ejaculatory duct. In men who are diagnosed with non-obstructive azoospermia, a testis biopsy may be performed to identify the predominant pattern of the testicular histology. Surgical procedures such as Testicular Fine Needle Aspiration (TFNA), Percutaneous Epididymal Sperm Aspiration (PESA), Microsurgical Epididymal Sperm Aspiration (MESA), Testicular Sperm Extraction (TESE), and Microdisection Testicular Sperm Extraction (TESA) offer infertile men who in previous years were unable to produce a biological child the possibility of fathering biological

children. Among men with a blockage, in nearly 100% of cases, surgical

procedures for sperm extraction are successful. In approximately 40% of non-

obstructive azoospermia cases, a few sperm cells are identified during the

Testicular Sperm Extraction (TESE). In some cases, the testicle may produce

only a few sperm. However, even if only a few sperm are found, they can be

used in ART procedures such as ICSI. In male infertility patients with tubular

sclerosis, maturation arrest, or Sertoli cell-only syndrome, mature spermatids or

testicular spermatozoa can be recovered in approximately 50% of the cases.

However, new innovations and research in micromanipulation such as with

Round Spermatid Nuclei Isolated (ROSNI) are providing these men with

prospects to father a biological child in the future (Speroff et al., 1994; Seibel,

1993, 1997; Sofikitis et al., 1995; Schlegel & Girardi, 1997; Johnson et al., 1999;

Pernoll, 2001; Goldstein et al., 2003;).

Artificial Insemination

John Hunter performed the first artificial insemination with the husband's

sperm intravaginally in England during the late 18th century. His nephew

reported a normal pregnancy and delivery as a result of this procedure. As early

as the beginning of the 1950s, reports of the use of AI with the husband's sperm

were published. Artificial Insemination is a rapidly advancing science and a

relatively simple procedure in which specially treated sperm from the male

partner are injected into the female's reproductive tract. The indications for AI

have been classified into five categories:

1. Mechanical problems in the male such as impotence, hypospadias, premature or retrograde ejaculation,

2. Mechanical problems in the female such as vaginismus or prolapse,

3. Cervical "hostility",

4. Poor semen quality in terms of either volume, concentration, motility, morphology, or the presence of antibodies, and

5. Idiopathic subfertility (Nuojua-Huttunen et al., 1995, 1997, 1999; Kovacs & Vollenhoven, 1997).

While AI is generally performed with the husband's sperm for most couples, using donor sperm is considered a treatment option for couples when the husband's ejaculate contains few or no live sperm or when he is genetically or anatomically unable to produce any sperm. Indication for the use of therapeutic donor insemination (TDI) is the absence of sperm sufficient in quantity or quality to be likely to produce a pregnancy. While TDI is an option for these couples, new assisted reproductive techniques can now provide alternative treatment options for many men who previously had been considered irreversibly subfertile. TDI may also be a treatment option for those men who are genetically and anatomically capable of reproduction but also have a genetic or psychological reason compelling him and his partner to request donor insemination. Other cases seeking donor insemination include the woman who has no sexual partner yet desires to have a child (Helsa, 1995; Kovacs & Vollenhoven, 1997).

Artificial insemination (AI) is a general term. Several different types of AI, which are named for the location of sperm insemination into the female, are available. One type is intracervical insemination (ICI); in this procedure, the sperm is injected into the female's cervical canal. ICI is an appropriate therapy to enhance fecundity in circumstances such as when intravaginal intercourse with ejaculation in their pericervical area is not possible or when the use of donor sperm is planned. Pregnancy rates for ICI treatment average 8 – 12% per treatment cycle. At least 60% of couples should conceive within six treatment cycles (Helsa, 1995; Nuojua-Huttunen et al., 1995, 1997, 1999; Kovacs & Vollenhoven, 1997).

Intrauterine insemination (IUI), the most common form of AI used, is a procedure where the sperm are injected into the female's uterine cavity. This method is particularly useful if the cause of infertility has been determined as an insufficient or hostile cervical mucus or low sperm count or motility. In circumstances where cervical mucus is insufficient or hostile, IUI is advantageous because it allows sperm to bypass the cervix completely. In cases where infertility is due to low sperm count or motility, IUI is advantageous because it places the healthiest sperm into the female tract to increase the likelihood that one of those sperm will fertilize an egg. Although IUI is relatively uncomplicated and less invasive than ART procedures, one disadvantage associated with IUI is that it does not allow the physician to evaluate whether or not fertilization is capable of taking place. Although IUI is a more natural method of conception than ART procedures, whether or not the sperm actually fertilizes

the egg to make an embryo is unknown unless the woman becomes pregnant after the first IUI cycle. The pregnancy rates for IUI treatment cycles range on average between 15 – 20% per cycle. If all other conditions affecting fertility are thought to be normal or adequately treated, then a reasonable length of treatment time with IUI is about three to six treatment cycles (Helsa, 1995; Nuojua-Huttunen et al., 1995, 1997, 1999; Kovacs & Vollenhoven, 1997).

Other methods of AI include Direct Intraperitoneal Insemination (DIPI), Transuterine Intratubal or Semen Intrafallopian Insemination (SIFT), and Direct Intrafollicular Insemination (DIFI). Manhes and Hermabessiere initially described DIPI in 1985. This AI technique is a process in which sperm are introduced into the body cavity between the uterus and the rectum around the time of ovulation. This procedure has been described as useful for certain categories of infertility such as cervical factor or male subfertility. Transuterine Intratubal or SIFT has been made possible by the development of catheters capable of being inserted through the uterus and placed in the ampulloisthmic region in an atraumatic fashion. This technique is a sonographically guided procedure in which sperm washed free of seminal fluid are injected into the fallopian tubes. This procedure has been suggested as a means to reduce the total number of motile sperm required for the insemination or as a means to decrease the need for superovulation in subfertile couples. In Intrafallopian insemination the sperm are injected directly into the female's fallopian tubes. Finally, DIFI is a technique in which the sperm are injected into the female's ovarian follicle under ultrasound guidance transvaginally. Note that any of the AI procedures may also be

combined with other treatment options such as ovarian stimulation through hormone therapy or following surgical procedures (Helsa, 1995; Nuojua-Huttunen et al., 1995, 1997, 1999; Kovacs & Vollenhoven, 1997).

Assisted Reproductive Technology

ART procedures include any technique in which both the oocytes and sperm are handled or manipulated outside of the body. ART procedures are generally the last treatment option for those couples for whom other less invasive and expensive treatments have been unsuccessful. The most commonly performed and recognized ART procedure for treating infertility is in-vitro fertilization (IVF). In 1976, Edwards and Steptoe first described the technique for in vitro fertilization (IVF) and embryo transfer (ET). In 1978, their work resulted in the birth of two normal babies and represented a major milestone in infertility treatment. Their success dramatically changed the treatment options for infertile couples. IVF is a procedure in which fertilization occurs in vitro outside of the woman's body in a laboratory. The man's sperm and the woman's egg are combined in a laboratory dish. The resulting embryo is then transferred to the woman's uterus. The five basic steps in an IVF treatment cycle are ovarian hyperstimulation, egg retrieval, fertilization, embryo culture, and embryo transfer. A treatment option for couples with various types of infertility, since IVF allows the doctor to perform in the laboratory what is not happening naturally. Initially, IVF was only used for female tubal factor infertility such as blocked, damaged, or absent fallopian tubes. Today, IVF is used to circumvent infertility caused by practically any problem, including endometriosis; immunological problems;

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unexplained infertility; and male factor infertility (Damewood, 1995; Laufer et al., 1997; Talbot & Lawrence, 1997).

In 1984, gamete intrafallopian transfer (GIFT), designed for women with idiopathic infertility, was first used in humans. At that time, GIFT provided a much better pregnancy rate and is considered a more natural method of conception than other ART procedures. GIFT is a procedure in which the female patient undergoes a controlled ovarian hyperstimulation. The oocytes are retrieved transvaginally using ultrasound guidance. Three to 4 oocytes are then placed via laparoscopy into one of the fallopian tubes along with the sperm. One of the disadvantages of the GIFT procedure has been the transfer of sperm and oocytes into the fallopian tube via laparoscopy necessitating abdominal incisions and anesthesia. Consequently, some authors have suggested the use of hysteroscopic techniques in which the gametes are transferred into the fallopian tubes via a transcervical tubal catheterization (Balmaceda et al., 1995; Dlugi et al., 1997; Wood, 1997).

Modifications of the GIFT procedure include Zygote intrafallopian transfer (ZIFT) and tubal embryo transfer (TET). ZIFT is used primarily for couples with severe male factor infertility. In this procedure, the female patient undergoes a controlled ovarian hyperstimulation and the oocytes are retrieved in a similar fashion as in GIFT. However, unlike GIFT, the oocytes are allowed to fertilize in vitro in the laboratory. At the 2-pronuclear stage, which usually occurs 24 hours later, 3 to 4 embryos are then transferred via laparoscopy into one of the female's fallopian tubes. If the embryos are allowed to develop beyond the 2-cell

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stage, the procedure is then termed a tubal embryo transfer (TET). The only

benefit to performing ZIFT or TET versus the tradition IVF procedure is for

women who are thought to have compromised embryo quality due to embryo

culture in vitro. The prevailing belief is that placement of the zygotes or embryos

back into their own natural incubator, the fallopian tube, will enhance subsequent

development, will be enhanced leading to improved pregnancy rates (Balmaceda

et al., 1995; Dlugi et al., 1997; Wood, 1997).

In 1992, the first pregnancies and births resulting from Intracytoplasmic

sperm injection (ICSI) were reported. ICSI is the preferred ART procedure for

couples in which the male partner has azoospermia, severe oligospermia, or

severe defects of sperm shape known as teratospermia. This treatment option is

also recommended for those men with significant antisperm antibodies, low

sperm motility, or significant sperm morphology. The final indication for the use

of ICSI is when poor fertilization occurs with regular insemination techniques in

the laboratory. In this procedure, sperm are obtained either from the ejaculate or

directly from the epididymis or testicle through surgical procedures such as

TFNA, PESA, MESA, TESE, or TESA. As with IVF, the female patient

undergoes controlled ovarian hyperstimulation and egg retrieval is performed. A

single spermatozoon is injected through the zona pellucida directly into the

oocyte. Once fertilization has taken place, the embryos are then transferred into

the woman's uterus (Steirteghem, 1995; MacLachlan, 1997).

Finally, preimplantation genetic diagnosis (PGD) is currently being offered

to couples receiving IVF and ICSI treatments. PGD is a technique that combines

recent advances in genetic research and reproductive medicine and examines

the early embryo after ART procedures such as IVF for inherited diseases or to

determine the sex of the embryo for sex-related genetic disorders. In 1968,

Edwards and Gardner successfully performed the first known embryo biopsy on

rabbit embryos (Edwards & Gardner, 1968). Subsequent to this research,

preimplantation genetic diagnosis for humans was developed in the United

Kingdom during the mid 1980s. In 1989, Handyside and his colleagues refined

the procedure and reported the first unaffected child born following PGD

performed for an X-linked disorder. As of May 2001, more than 3,000 PGD

clinical cycles have been documented and nearly 700 children have been born,

demonstrating the reliability and safety of this procedure. The process is

performed with ART procedures such as IVF where an embryo develops in a

laboratory. When the embryo is at the 6 to 8-cell stage of development, 1 to 2

cells are removed. These cells are then sent to a genetics laboratory for

diagnosis using either polymerase chain reaction (PCR) or fluorescence in situ

hybridization (FISH) techniques. The embryos unaffected by genetic disorders or

disease are then transferred into the woman's uterus. By transferring only the

unaffected embryos, adverse outcomes such as miscarriages, pregnancy

termination following prenatal diagnosis, or birth defects can be prevented. PGD

is useful for identifying three major groups of disease. Chromosomal disorders

include a variety of chromosomal rearrangements, including translocations and

inversions and deletions. PGD is also used to identify single gene defects

including cystic fibrosis, Tay-Sachs disease, sickle cell anemia, and Huntington

disease. Finally, PGD is useful for determining the sex of an embryo in which the

specific genetic defect at a molecular level is unknown, highly variable, or

unsuitable for testing on single cells. Disorders such as hemophilia, fragile X

syndrome, neuromuscular dystrophies, and hundreds of other diseases can be

identified through PGD. Sex-linked dominant disorders include Rett syndrome,

pseudohyperparathyroidism, incontinentia pigmenti, and vitamin D-resistant

rickets (Handyside et al., 1989; Flinter, 2001; Harper, 2001).

ART Success Rates. Since the first infant was conceived from in vitro

fertilization (IVF) in 1983 in the United States, the use of IVF and assisted

reproductive technology (ART) has increased substantially. The 1992 Fertility

Clinic Success Rate and Certification Act direct all U.S. clinics performing ART

procedures to report data annually to the CDC for every ART procedure initiated.

ART is defined as any fertility procedure in which both oocytes and sperm are

handled outside the body. Therefore, information regarding the number of

clinics, cycles performed, live-birth deliveries, and total number of live babies

born as a result of in-vitro fertilization (IVF), gamete intrafallopian transfer (GIFT),

and zygote intrafallopian transfer (ZIFT) procedures is collected by the CDC

through the Society for Assisted Reproductive Technology reporting system. To

date, six reports have been published under the Fertility Clinic Success Rate ad

Certification Act, the latest of which was in 2000. In the 2000 report, 98 percent

of ART procedures include IVF stimulated cycles, while the remaining two

percent include GIFT and ZIFT treatment approaches and shows that the

number of ART clinics, cycles performed, live-birth deliveries, and total number of

live babies born as a result of ART have steadily increased since 1995. The number of infertility clinics in the United States has grown from five in 1982 to 383 in 2000. The number of ART cycles performed in the United States increased 54 percentage points overall from 64,724 ART cycles 1996 to 99,639 ART cycles in 2000. In addition, the number of live birth deliveries increased from 14,573 in 1996 to 25,228 in 2000, representing an increase of 73 percent. The number of live babies born as the result of ART increased 67% overall, from 20,921 born in 1996 to 35,025 born in 2000 (Abma et al., 1997; Wright et al., 2003; CDC 2002).

Although the National IVF Registry records information on all treatment approaches in which both oocytes and sperm are handled outside the body including IVF, GIFT, and ZIFT, the number of couples seeking other treatment options such as IUI is not as readily available. However, the NSFG does collect information regarding the number of women who seek treatment for infertility as well as the type of treatment received. Findings of the NSFG show that the use of infertility services and treatment increased steadily from 1982 to 1995. Of the 60.2 million women of reproductive age in 1995, 9.3 million reported having used some kind of infertility service at some time as compared to 6.8 million in 1988. Among childless women aged 35-44, 21 percent reported having used infertility services. The most common infertility services received by these women included medical advice, diagnostic testing and evaluation for either the woman or man, and ovulation inducing medications (Abma, 1997; Wright et al., 2003; CDC 2002).

Associated Costs and Insurance for ART. By the end of 2000, more than 212,000 babies have been born in the United States as a result of reported ART procedures. IVF currently accounts for approximately 98% of the ART procedures with GIFT, ZIFT, and a combination representing the remaining 2% of procedures being conducted. However, ART procedures are the most expensive infertility treatment procedures performed. Reports of the average cost of one IVF cycle in the United States range between $8,000 and $12,400. While IVF and other ART procedures are not inexpensive, they account for 0.03% of U.S. health care costs. In 1988, the U.S. Office of Technology Assessment (OTA) published a study on the medical and social aspects of infertility. In this study, the estimated total infertility expenditures nationally for 1987 were $1.0 billion. OTA provided a categorical breakdown of infertility treatment into the following four typical stages:

1. Diagnosis and fertility drug treatment,

2. Complete evaluation of both partners,

3. Tubal surgery, and

4. In vitro fertilization.

The average cost of the first stage of treatment was reportedly $3,668; the second stage was $2,055; the third stage was $7,118; and the fourth and final stage was $9,376 (Ryan, 2001; RESOLVE, 1998-2003; ASRM, 2002-2003).

ART in the United States is largely a fee-for-service, private market business. Because most insurance companies offer only partial coverage or none at all, an average of approximately 85% is the patient's share of costs for

IVF and IVF-related therapies in the United States, while a patient share of costs in France is approximately 7% and 15% to 28% in Canada. One consequence of this privatization is that access to ART procedures is determined principally by financial status. Although some ART providers limit access to IVF to married couples using their own gametes or to women under forty and others exclude single women or gay or lesbian couples, in general, the type and extent of treatment are primarily governed by how much the patient is able and willing to spend. As a result, there is a marked disparity between the population of infertile couples in the United States and those who are receiving services (Ryan, 2001).

Although no federal law requires insurance coverage for infertility treatment, to date, 15 states have enacted some type of infertility insurance coverage law. While each law is unique, these laws require insurers to either cover or offer to cover some form of infertility diagnosis and treatment. For states mandating coverage, health insurance companies are required to provide coverage of infertility treatment as a benefit included in every policy. In states mandating the offer for coverage, health insurance companies are required to make available for purchase a policy that offers coverage of infertility treatment. However, the law does not require employers to pay for the infertility treatment coverage; instead employees may be offered coverage as a rider to the insurance policy. In addition, coverage for infertility services varies from state to state. While some states require only that in vitro fertilization treatments be provided by insurance, others specifically exclude coverage for this treatment. State law mandating employers to cover infertility and related services currently

include Arkansas, Hawaii, Illinois, Maryland, Massachusetts, Montana, New Jersey, Ohio, Rhode Island, and West Virginia. States mandating that employers offer coverage include California, Connecticut, and Texas (RESOLVE, 1998-2003; ASRM, 2002-2003).

Currently, RESOLVE, a national infertility patient advocacy and information organization, is working with members of Congress on legislation requiring insurance coverage of infertility treatments. Legislation currently being introduced includes:

- The Family Building Act of 2003 (HR 3014) introduced by Representative Anthony Weibner and would require insurance coverage of infertility treatments, including up to 4 IVF attempts, by all group health plans that also cover obstetrical benefits. In addition, coverage in self-insured health plans would also be required.

- HR 3026 is legislation sponsored by Representative Marty Meehan to require health plans available to federal employees, military personnel and their families to cover infertility treatments.

- HR 969, sponsored by Representative Rob Andrews would require Medicare coverage of infertility treatment services for those entitled to health insurance benefits under that program by reason of a disability.

- The Equity in Fertility Coverage Act of 2003 (HR 1852) sponsored by Representative Rob Andrews would require all health plans that cover Viagra, and similar medications, to also cover infertility treatment (RESOLVE, 1998-2003; ASRM, 2002-2003).

Mandating coverage for infertility treatments is a controversial issue.

Infertility treatment, when it is covered at all, is generally limited to the diagnosis

or diagnosis and treatment of correctable medical conditions. Insurers have

justified exclusions of providing coverage of IVF on several grounds. Advocates

for mandating infertility treatment coverage argue that infertility is a physical

problem that could be corrected medically and therefore that patients presenting

with this condition should be afforded the same health care rights as those who

suffer from illnesses such as diabetes; opponents contend that infertility is not an

illness. Insurers typically employ a broad understanding of the term "illness".

This term includes "diseases" or conditions such as chemical dependency,

congenital defects, alcoholism, hernias, headaches, senility, exogenous obesity,

etc. In addition, since the majority of insurance carriers cover at least some

infertility services such as diagnostic testing and surgical correction for

endometriosis, the argument that infertility should not be defined as an illness

may be viewed as arbitrary and inconsistent. Secondly, opponents of mandating

insurance coverage that includes treatments such as IVF argue that IVF is not

medically indicated because the procedure does not correct the underlying

medical problem. However, in *Ralston v. Connecticut General Life Insurance*

Company, the court defined the standard for inclusion of a treatment for

coverage as evidence demonstrating that the treatment works as well as or

better than presently available methods. In addition, it was noted that consistent

application of this principal asserted by insurance companies would require the

denial of coverage for any treatment that merely compensates for or replaces

any impaired or lost bodily function such as kidney dialysis, coronary bi-pass surgery, limb prosthesis, etc. Finally, opponents argue that IVF is an experimental therapy. In the *Reilly v. Blue Cross and Blue Shield United* case in 1988, the courts agreed with the insurer's argument that a treatment with success rates less than 50 percent could be considered an experimental treatment. However, advocates for mandated insurance coverage laws contend that consistent application of this principal would lead to exclusions of treatments typically provided to terminally ill patients since such cases have a zero success rate. In addition, advocates for mandatory insurance coverage of infertility treatment contend that since infertile couples pay premiums for health insurance benefits such as maternity services that they are unable to use, infertility services should also be covered by their health plan. However, opponents argue that the addition of this benefit increases the premiums for a larger number of people as compared to the number of people who will take advantage of this benefit and, therefore, that the increased costs for covering these procedures are unjust. In addition, employers and insurers contend that requiring coverage for infertility services, treatment or procedure, increases the overall cost of insurance, resulting in an increased number of uninsured. Rebutting this argument, however, is a study conducted by Griffin and Panak who examined the actual costs of providing coverage for infertility, including IVF, and found that under Massachusetts' mandate for group coverage plans, the increase in annual premium per person was $1.71 per month (Ryan, 2001; RESOLVE, 1998-2003; ASRM, 2002-2003).

Legal and Ethical Considerations for Infertile Couples and ART. In

American society, there is a strong legal and moral basis for the protection of

autonomy in reproductive decisions. Decisions made by individuals and couples

about whether or when to produce children are thought to be a matter of personal

private concern, not a subject for governmental legislation. These decisions are

protected by the U.S. Constitution as the right to privacy, has evolved through

case law and has been supported by judicial decisions as early as 1942. In

Skinner vs. Oklahoma, the U.S. Supreme Court overthrew an Oklahoma statute

authorizing the sterilization of habitual criminals convicted of crimes of moral

turpitude. In this decision, the court stated:

> "[W]e are dealing with legislation which involves one of the basic
>
> civil rights of man. Marriage and procreation are fundamental to
>
> the very existence and survival of the race…" (Skinner v Oklahoma,
>
> 1942).

This decision was followed by a series of cases involving contraception

and abortion that further delineated how an individual's decision whether or not to

have children was constitutionally protected from governmental interpretation.

Legislative rulings defined the right to conceive and produce children as "far

more precious than property rights." The constitutional right to privacy as

recognized by the American judicial system, protects decisions to reproduce

coitally because of the biologic and social importance placed on parenting.

Furthermore, reproductive autonomy is extended to decisions to reproduce using

alternative methods. For governmental regulation interfering with reproductive

decisions to be upheld as constitutional, such regulation must be necessary to further a compelling state interest and must regulate in the least restrictive manner possible. This right to privacy serves as the setting in which governmental actions and legislation must be measured. This right constitutes the basis on which health care professionals and infertility patients can challenge legislation that prohibits or restricts research and clinical practice in the area of assisted reproduction (Andrews & Hendricks, 1987).

Although ART procedures are often the last hope for some couples to conceive a child, many ethical and moral issues must be considered before embarking on such an invasive treatment plan. Ethical considerations regarding infertility treatment include issues such as the use of donor sperm, donor oocytes, and donor pre-embryos. Issues regarding treatment options can be particularly difficult for infertile couples to resolve within their moral and personal belief systems. Other issues that confront infertile couples include the cryopreservation of oocytes and pre-embryos and more specifically, what should be done with any unused oocytes and pre-embryos. The latest procedure, preimplantation genetic diagnosis (PGD), may also provide ethical dilemmas to infertile couples. Because PGD provides physicians with the ability to select only the healthiest pre-embryos for implantation, this may conflict with a couple's ethical and moral beliefs about the sanctity of all life. In addition, issues regarding the use of PGD for the selection of a specific gender have evolved. Not only do couples have to weigh these infertility treatment options against their personal ethical belief systems, but they must also grapple these decisions with

their religious teachings and convictions (Andrews & Jaeger, 1997; Schenker, 1997; Seibel et al., 1994; Quinn et al., 1997; Zilberstein & Seibel, 1997).

Conceptualization and Operational Classifications of Stress

While couples often describe infertility as the most stressful experience of their lives, the stress associated with infertility is only one topic within a huge field of stress research. Public and scientific interest in the relevance of stress to health and disease developed shortly before World War II. One measure of the perceived importance of this issue is the amount of money and attention given to combating the effects of stress. Executive management courses and many other self-help programs as well as a wide range of books aimed at preventing or alleviating stress-related problems have become a thriving industry. In addition, stress-related medical complaints have helped to make antianxiety medications some of the most widely prescribed medications in the United States (Elliott & Eisdorfer, 1982). Along with public interest, the proliferation of stress and stress-related literature provides evidence of heightened scientific interest in the concept of stress. Research on stress and the effects of stress has reached an all-time peak during the past two decades (Goldberger & Breznitz, 1993).

Although stress has become a common topic of research, no one has formulated a definition of stress that satisfies even a majority of researchers. Controversies regarding the conceptualization of stress and stress related research plague the field. While some scientists believe that the conceptualization of stress has become over-generalized, other scientists believe that the broad conceptualization of stress provides an invaluable unifying

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terminology for a particular type of important research (Elliott & Eisdorfer, 1982).

However, Pearlin, Lieberman, Menaghan, and Mullan (1981) suggest that the

core meaning of the concept of stress is not confusing. They assert that there is

general agreement that the term stress refers to a response of the organism to a

noxious or threatening condition. The confusion and disagreement arise with

regard to where and how to identify this response. Is stress to be identified by

the functioning of an organ or a system of organs, by biochemical or

physiological response patterns, by changes in emotional states, or by the

presence of illness or disease entities? Other debatable dimensions of stress

arise with respect to the duration, individual perception, and situational context.

For example, is stress manifested in short-term reactions of the organism or in

long-term dysfunctions? Are individuals aware of the stress they harbor to the

extent that they can report it or must the presence of stress be determined by

independent measures? Is stress a global, encompassing state, or is it confined

to specific situations or contexts in which it is aroused? According to Pearlin

(1993), one problem in defining and understanding stress is that the nature of

stress is a diffuse and multidimensional phenomenon and can mean so many

different things. The many different conceptualizations of stress that exist in

research appear to meet specific needs within a given context of research.

However, stress tends to be characterized in three broad categories: systemic or

physiological, psychological, or social. Systemic or physiological stress is

concerned primarily with the disturbances of tissue systems. Psychological

stress focuses on cognitive factors leading to the evaluation of a threat. Social

stress is defined by the disruption of a social unit or system. While many agree

that the three types of stress are related and overlap in various ways, the nature

of their relationships is far from clear (Monat & Lazarus, 1977; Pearlin, 1993).

Within these three categories of stress, basic themes emerge in the

research literature. Common among all research related to stress is the

identification of stressors. Stressors are defined as external events or conditions

that affect an organism. In human research, the investigation of the impact of a

given stressor on an individual is widely studied within the context of the

cognitive appraisal of stressors. In accordance with Lazarus's formulation,

cognitive appraisal plays a vital role in the transaction between the person and a

potentially stressful environment. Researchers are largely interested in the

effects of stress. Research investigating the effects of stress includes a wide

range of impacts from minor changes in behavior to dramatic clinical symptoms.

Another common theme in stress research relates to coping. After an individual

appraises a situation, the individual will use one or more coping strategies in an

attempt to adjust the environment or situation. Within the stress literature,

studies investigating the various coping strategies encompass a large body of

research (Goldberger & Breznitz, 1993; Selye, 1993).

In July of 1979, the Office of Science and Technology Policy (OSTP),

Executive Office of the President, requested a "definition of research issues,

delineation of desirable and adverse aspects of stress in its various forms, and

biomedical, behavioral, and sociological approaches to the description and

alleviation of excessive stresses". Several other agencies supported this

research including the National Science Foundation (NSF), the Office of

Prevention of the National Institute of Mental Health (NIMH), and the National

Institute on Aging (NIA). The National Academy of Sciences' Institute of

Medicine accepted this daunting project. Their study titled "Research on Stress

in Health Disease" indicated a strong bias in stress research. Their review of the

stress literature revealed that many stress researchers have emphasized mainly

adverse consequences of stress, confirming many people's conceptualization of

stressors as being inherently "bad". That stressors and reactions to stressors

produce a wide range of consequences, only some of which may be undesirable,

was highlighted through this study. Focusing more attention in the literature and

future research on the positive consequences associated with stressors was

advocated (Elliott & Eisdorfer, 1982).

Theories of Stress

The foundation for modern theories of stress can be traced back to

ancient Greece. Hippocrates, often considered the "father of medicine", clearly

recognized the existence of the healing power of nature comprised of inherent

mechanisms of the body for restoring health after exposure to pathogens.

However, early investigations conceptualized stress as being inherently

unpleasant rather than encompassing experiences with both positive and

negative outcomes. In 1879, the French physiologist Bernard advanced this

subject by pointing out that the internal environment of a living organism must

remain fairly constant despite changes in the external environment. Bernard's

pioneering studies on the particular adaptive changes by which the steady state

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is maintained provided the foundation for later research. During the early 1900s,

Cannon, an American physiologist, coined the term "homeostasis" from the

Greek *homoios*, meaning similar, and *stasis*, meaning position. This term

referred to "the coordinated physiologic processes, which maintain most of the

steady states in the organism" (Cannon, 1939). In his work on blood hormones,

Cannon frequently studied the effects of physical or emotional "stress" defined as

stimuli that disrupted an individual's normal internal environment. In totality,

Cannon's studies established the existence of many highly specific physiological

mechanisms for protection against a variety of threats to a body's constant state.

In particular, he emphasized the stimulation of the sympathetic nervous system

and the resulting hormonal discharge from the adrenal glands. The stimulation of

the sympathetic nervous system occurs during emergencies such as pain or

rage. In turn, this autonomic process induces the cardiovascular changes that

prepare the body for flight or fight. This research provided the foundation for

stress research and the resulting theories of stress (Selye, 1977, 1993; Elliott &

Eisdorfer, 1982).

Most current stress models are based on the conceptualization of stress in

three distinct ways. The first approach conceptualizes stress as a physiological

adjustment process and views stress as an internal response. In the second

approach, stress is characterized as an external or situational stimulus.

Proponents of this model attempt to describe the characteristics of a stressful

environment as well as the particular stimuli that produce stress. The third

conceptualization of stress is a synthesis of the first two approaches. While

circumstances may be intrinsically stressful, psychological process such as perceptions of abilities, needs, personality, and resources interact with the external events and stimuli to produce a variety of responses. In this interactive approach, the pivotal concept is that individuals are active agents who continuously cognitively appraise themselves and their environment and evaluate the fit or misfit between these variables. When perceived environmental demands exceed the individual's perceived response capability or when the environment is not able to meet the individual's internal needs and values, an individual's stress increases (Lazarus, 1966; McGrath, 1970).

The first conceptualization of stress as a response arose from physiological research. One of the most popular models conceptualizing stress as a response is the General Adaptation Syndrome (GAS). The popularity of this line of stress research can arguably be attributed to the work conducted by Hans Selye. While attempting to discover a new sex hormone, Selye discovered that rats receiving multiple doses of a crude ovarian extract developed many physical maladies including enlargement and hyperactivity of adrenal glands, involution of the thymus and lymph glands, and gastric ulcers. It was later discovered that all toxic substances, irrespective of their source, elicited the same pattern of physical responses. In addition, he documented identical organ changes evoked by stimuli such as cold, heat, infection, trauma, hemorrhage, nervous irritation, and many other stimuli. These changes were identified as objective indices of stress and furnished the basis for the development of his stress concept. He suggested that individuals exposed to a noxious stimulus responded with what

he referred to as the general adaptation syndrome (GAS) or the biologic stress syndrome. Three stages are identified in the GAS. The first stage is the alarm reaction, in which adaptation has not yet occurred. Selye asserts that this stage probably represents the somatic expression of a generalized call to arms of the body's defense forces. During the alarm reaction, the cells of the adrenal cortex discharge their secretory granules into the bloodstream and thereby become depleted of corticoid-containing lipid storage material. The second stage is the stage of resistance, in which adaptation to the stressor is optimal. During this stage, the cortex becomes particularly rich in secretory granules. Evidence of the body's adaptation is demonstrated through hemodilution, hyperchloremia, and anabolism, with a return to normal body weight. The final stage in this model is the stage of exhaustion, in which the acquired adaptation is lost again. This stage follows the stage of resistance as long as the demand is severe enough and applied for a sufficient length of time. This stage exemplifies that the body's ability to adapt is finite, since, under constant stress, exhaustion eventually ensues (Selye, 1966, 1977, 1993; Dohrenwend & Dohrenwend, 1980; Elliot & Eisdorfer, 1982). Selye later revised the GAS stating that organismic stress is basically the same regardless of the type of stressor and described two distinct types of stress: eustress and distress. Eustress is defined by Selye as "good" stress such as commitment to accomplishment while distress was viewed as "bad" stress such as frustration and resentment. According to Selye, distress is destructive to health while eustress is not (Lazarus et al., 1980; Selye, 1977, 1993).

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While stress research expanded through Selye's work on physiological responses to stress, research on the psychological effects of major life events received increasing attention with the publication of the Holmes-Rahe scale of life-change events in 1967. Life events are defined as objective experiences that disrupt or threaten to disrupt an individual's usual activities, causing substantial readjustment in their behavior. The foundation of life-events research is established in the work completed by Cannon. Through his research, Cannon demonstrated that emotion-provoking stimuli could produce the physiological alterations necessary for "fight or flight". He further proposed that physical illness would result with long or persistent stimuli producing such physical reactions. Adolf Meyer modified this argument during the 1930s by asserting that ordinary, normative changes in patients' lives such as births, deaths, and job changes may play a part in the etiology of disease. The work conducted by Meyer and Selye gave legitimacy and impetus to studies examining not only reactions to physical stimuli, but also to studies of psychological stimuli as potential stressors (Thoits, 1983).

Theories of psychological stress center on negative emotions such as anger, fright, anxiety, shame, guilt, sadness, envy, jealousy, and disgust. However, it is recognized that positive emotions including happiness, pride, relief, and love can present some mediating effects (Lazarus, 1993). One of the main distinctions between psychological levels of stress as compared to stress at the physiological levels is the presumption that cognitive activities such as evaluative perceptions, thoughts, and inferences are used to interpret and guide every

adaptational interchange with the environment. In this conceptualization of

stress, an individual is said to appraise each ongoing and changing transaction

with the environment. This appraisal includes judgments about environmental

demands and constraints as well as resources and options available for

managing them (Lazarus et al., 1980). These conceptualizations of stress have

developed into a cognitive-motivational-relational theory that highlights the

importance of emotions in stress research (Appley & Trumbull, 1977; Lazarus,

1993; Strelau, 1995). Within this theory lies the assertion that emotions are

organized psychophysiological reactions to information and knowledge.

Although Duffy (1941) argued that emotion is an unnecessary concept because it

refers to activities that are not different from life itself, concerned with adapting to

the demands, constraints, and opportunities of living, Lazarus (1993) contends

that emotions are different from many other adaptational activities because they

are characterized by active psychobiological involvement in what is happening.

Furthermore, Lazarus asserts that with emotion, an individual has a vested

interest in the outcome (Appley & Trumbull, 1977; Lazarus, 1993).

    In the cognitive-motivational-relational theory, relational refers to the

metatheoretical assumption that emotions are always about the relationship

between the person and environment as opposed to environmental demands or

individual needs and processes. This theory defines emotion as an interaction

through an event creating personal harm, threat, or benefit on which the

emotions are predicated. The principle underlying motivation in emotion is that

emotions are reactions to the status of an individual's goals in everyday

encounters and in the individual's life overall. The term "motivational" refers to

the hierarchies of importance for goals that an individual brings to any event.

The transactions that take place in a particular situational context activate these

goals as stakes in the outcome of the event and generate new goals. The final

component of this theory refers to the cognitive knowledge and appraisal of what

is happening during an event. While knowledge consists of a set of beliefs,

which are either situational or generalized across situations about how the world

works, appraisal is an evaluation of the significance of what is happening in

terms of one's well being. Appraisal is essential in the generation of emotions

because it concerns an individual's personal stake in an encounter or event. The

quality and intensity of emotions depend on subjective evaluations or cognitive

appraisals of how an individual is doing with respect to their goal commitments

both short-term and long-term. In addition, the tendencies of an individual to act

are generated by their cognitive appraisals, which, in turn, influence an

individual's emotional reaction (Appley & Trumbull, 1977; Lazarus, 1993; Strelau,

1995).

According to Lazarus (1993), emotions are salient cognitive-motivational-

relational configurations within the person-environment relationship and are

shaped by the understanding and evaluation of this relationship by the individual.

In addition to the theoretical framework including emotions in stress research,

Lazarus defined distinctive patterns of appraisal for individual emotions. As

defined by Lazarus (1993), the central theme of anger is a demeaning offense

against an individual, which depends on the individual's appraisal that their self-

esteem is at stake in an encounter. According to Lazarus (1993), anger arises

when an individual is treated as less than he or she would wish. Anger is elicited

whether or not the intent is malevolent, but especially when it is. Those

individuals with a vulnerable self-esteem become angry more quickly than others

because it is difficult for them to wave off the attack as unimportant. Although

Lazarus (1993) described the action tendency of anger is to attack through

retaliation or vengeance, Averill (1983) revealed that the episodes of anger

reported by college students rarely involved an actual attack. Lazarus concedes

that anger is regarded ambivalently in our society: on the one hand, anger is

self-preservative; on the other hand, anger may be socially destructive (Lazarus,

1993).

Many researchers and theorists regard anxiety as an emotional result of a

threat to an individual's well being and to the essential meanings that comprise

that sense of well-being. When a threat is presented to an individual and the

threat is ambiguous, in other words, the individual does not know what will

happen, when it will happen, and therefore, does not know what is to be done

about it; then the emotional response is said to be anxiety. In addition, even

when the threat is concretized and externalized, the concrete condition

represents the more existential questions of who we are and what life meanings

we hold. With anxiety, when one such threat has been dealt with, another threat

always comes in its wake. Distinguished by this pattern, anxiety is an emotion

different from all others. Because of this unique pattern, theories of

psychopathology often center on anxiety and more specifically on inappropriate

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ways of coping with anxiety as the basic cause of psychopathology. Anxiety is produced when meaning and ideas are at stake. A threat to these meanings and ideas creates goal incongruence. If something or someone is held accountable for the threat, then the emotion is not anxiety. While anger assesses blame to something or someone else, anxiety is unique in that there is no blame to place elsewhere. When blame is assessed to oneself and the individual believes that a moral or imperative has been transgressed, the emotion provoked is guilt. Similarly, shame assesses blame to oneself. However, shame is the resulting emotion when an individual believes he or she has failed to live up to an ideal or expectation. Unlike anger, shame and guilt, sadness is an emotion similar to anxiety in that no blame is assessed. As with anxiety, sadness is ambiguous. Ambiguity about sadness revolves around whether it should be classified as a mood or an acute emotion. However, sadness is described by Lazarus (1993) as a unique negative emotion producing a reaction to an irrevocable loss which creates goal incongruence. Furthermore, sadness comes at the end of the grieving process. When an individual has accepted that he or she is helpless to change the situation, accepting the loss as irrevocable, then the individual experiences sadness. Before the acceptance of a loss as irrevocable, the individual will experience a variety of other emotions, which focus on trying to restore or ameliorate the threat or loss including numbness, denial, anger, anxiety, guilt, or shame (Lazarus, 1993).

The conceptualization of stress in social contexts identifies modern man as the stress system while dominant stressors are derived from the social

environment. Responses to these stressors are principally alterations in perceptual, intellectual, emotional, and consciousness activities, while physiological changes are secondary. Social stress is defined by Brown (1980) as an unfavorable perception of the social environment and its dynamics. In addition, Brown asserts that nearly all psychosocial stress-related disturbances develop from an individual's perception of their social situation. Psychological and physiological disturbances believed to be caused by, related to, or aggravated by social stress include emotional, psychosomatic, organic, psychological adjustment, and sociological problems. The existence of such diverse and enumerated reactions to social stress has made the application of a specific term or descriptive definition labeling the major determinants difficult. The conceptualization of social stress, however, is similar to conceptualizations in psychological stress. Complex intellectual functions are assumed to be involved in reactions to social stress. The sequence of mental activities delineated by conceptualizations of social stress includes an individual's expectations, perceptions of the social environment, interpretation of disparity between expectations and perceptions, rumination, perceptual distortion, and cortical inhibition. Expectations are multi-dimensional, subjective activities. An individual's history and experiences shape a person's environmental and social expectations. In addition, expectations are determined by, modified by, and related to personal aspirations, and motives. Perception of the social environment is a global activity and is in large part determined by the individual's expectations. A number of events must be observed, associated, analyzed, and

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judged. An individual's perception of social situations is an interpretation and a mental construction of social events and their significance not only in present tense, but also in the past and future (Brown, 1980).

When a significant disparity between the expectations of an individual and their perception of the environment occurs, intense cognitive activity takes place. This activity has a direct effect upon both subjective sensations and physiological activities. The disparity represents a conflict between the emotions and appraisals of expectancy as well as the emotions and appraisals of denial or of a lack of satisfaction. Following the recognition of a disparity between expectations and perceptions of reality, mental activity begins both at the conscious and unconscious level in an attempt to resolve or understand the reason for the disparity. Problem solving activities aimed at developing coping devices or resistance to the perceived stress are activated. Rumination generates anxiety or apprehension which directly activates the physiological defense mechanisms resulting in muscle, visceral, and subjective tension. At the same time, rumination involves the almost constant creation and re-creation of the social context and problem as mental images. Along with these re-creations of the context and problem are projections of various alternative solutions into both past and future imagined situations. These images directly induce physiological activation. For example, the thought or image of eating a sour lemon leads may individuals to the production of saliva and other physiological responses. Likewise, conscious or unconscious images of anxiety-producing situations can excite physiological responses that mimic the original reactions. In addition, all

organs of the body respond to mental images involving those organs. With

certain predispositions, the images may produce any or all of the physiological

arousal responses accompanying anxiety (Brown, 1980).

Following rumination, perceptual distortion occurs when an individual's

attention becomes directed toward those elements or stimuli in the social

environment that are related to their mental construction of the problem. As a

result, a skewed perception develops in that the individual sees and hears

predominantly those things of the social dynamics that fit their preconceived

mental images of the situation and problem. This distortion intensifies the

significance and breadth of the problem while strengthening inappropriate

solutions, eventually leading to heightened levels of distress (Brown, 1980).

The final stage in this conceptualization of the stress process is referred to

as "cortical inhibition", a term coined by Hefferline. This stage occurs when an

individual's cognitive activity becomes more narrowly focused. At this stage,

normal homeostatic mechanisms regulating neural conduction of muscles and

viscera become impaired. These physiological responses reduce the subjective

appreciation of the cause and effect relationship of the tensions experienced by

the individual while at the same time increasing the sensation of tension from

unknown origin and physiological adaptation. The cortical inhibitory effect is

often inferred to indicate that a distortion in the individual's perceptions of social

reality takes place (Brown, 1980).

The sequence of mental activities from an individual's expectations to

perceptual distortion structure the cognitive activities that process social data in

such a way that elements of the social environment are interpreted as posing threats to an individual's well-being. Specifically, rumination generates both threats to well being along with emotional sensations and mental images which excite defense postures. These emotional sensations and mental images appear to be the primary psychological and physiological manifestations of the social stress response (Brown, 1980).

The conceptualization of psychosocial stress is a synthesis of psychological and social stress theories. Research into the psychosocial basis of psychological distress has a long history in the behavioral sciences. However, the focus of this research is limited to a number of specific areas. The majority of this research is primarily found in either ongoing interpersonal relationships or in discrete life events. According to Kaplan (1983), "psychosocial stress refers to socially derived, conditioned, and situated psychological processes that stimulate any or all of the many manifestations of dysphoric affect falling under the rubric of subjective distress" (p. 196). Likewise, in the conceptualization of psychosocial stress, psychological distress reflects an individual's inability to prevent or diminish perception, recall, anticipation, or imagination of devalued circumstances. The emphasis, however, is placed on the individual's cognitive and affective-evaluative interpretation of circumstances rather than on the circumstances themselves in the elicitation of psychological distress. There are three mutually influential psychological process components of psychosocial stress. The affective process refers to the individual's need – value structure that influences the individual's perception of reality and motivates the individual to

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behave according to valued states. Cognitive processes include the individual's

perception, recall, anticipation, and imagination of the situation or environment.

Finally, the attributes and responses of the individual and others constitute the

behavioral processes. These behavioral processes stimulate an individual's

subjective awareness which in turn stimulates the individual's need-value

system. The conceptual framework of psychological distress directly reflects an

individual's subjective perception of devalued circumstances. Subsequent to this

perception is the outcome of the influences on the individual's need-value

system, the occurrence of the circumstances that, from the perspective of the

individual's need-value system, are disvalued, and the perception of the

occurrence of the disvalued circumstances (Kaplan, 1983).

Measurements of Stress

In scientific investigations, the nature of the theories proposed frequently

dictate operational definitions of the constructs and boundaries of the conceptual

domain from which theories are derived. These operational definitions specify or

structure the nature of the measurement used to conduct investigations. While

stress research is no exception in this regard, the complex and sometimes

contradictory array of stress theories has resulted in a multitude of operational

formats for stress measurement. However, one of the primary modalities for

stress measurement is through self-reporting. Self-report measures of stress are

a predominant choice for researchers because so many of the popular theories

of stress emphasize intrapsychic cognitive processes such as the use of

appraisal and application of coping skills or emotional states such as anxiety or

depression as central themes to the definition of stress. Self-report measures of stress have been largely influenced by three classical approaches to theories of stress: stimulus-oriented theories, response-oriented theories, and interactional or transactional theories (Derogatis & Coons, 1993).

Because stimulus-oriented stress research focuses on the intrinsic potential for stress in the environment, measurements of stress derived from this approach address the significant characteristics of the environment that impinge upon the individual and include methods that differentially assign weights or quantify the stress value of the environmental stimuli. Unfortunately, few approaches have given rise to a consistent psychological measurement strategy. However, life events research is an exception to this trend. Modern research on life events can be traced back to the publication of the *Schedule of Recent Experiences* (SRE) developed in 1957. Research on the psychological effects of major life events has proliferated over the past few decades. Since World War II, the relationship between life events and psychological disturbance has been studied in three major ways:

1. Psychiatric effects of particular events such as marriage, the birth of a child, divorce, and death,

2. Psychological effects of multiple events in the lives of random samples of adults and children, and

3. Comparisons of the number and types of life events experienced by psychiatric patients prior to hospitalization to those experienced by nonpatient control groups.

The SRE originally contained 42 items and was regarded as a life events incidence measure. The earliest, best known, and most widely used approach to measuring life events is the Holmes-Rahe scale of life events (1967). Rahe (1974) modified this original set of items on the SRE and added 13 questions designed for prospective research on life change and illness. This instrument is known as the Recent Life Changes Questionnaire (RLCQ) (Derogatis & Coons, 1993). Since the development of this scale, a host of life events checklists have been developed, including the Psychiatric Epidemiology Research Interview (PERI) Life Events Scale. An alternative to these self-report instruments is the structured event probe and narrative rating method. This approach requires semi-structured interviews designed to elicit a detailed description of each life event and are then evaluated by independent raters (Dohrenwend et al., 1993.)

Numerous other scales have since been developed to measure life stress. In addition to the SRE and RLCQ, the Life Experiences Survey (LES) (Sarason, et al., 1979) and the Global Assessment of Recent Stress (GARS) (Linn, 1985) and many other innovative life stress measures have subsequently been developed. One criticism of these scales is that the events that comprise the scales are irrelevant for many subgroups of society. Current research is beginning to address this issue (Horowitz et al., 1977; Sarason et al., 1979; Blake et al., 1984; Linn, 1985; Dise-Lewis, 1988; Greenberg, 1990; Derogatis & Coons, 1993).

The work of Cannon (1932) and Selye (1994) has led to many response-oriented theories of stress. The majority of instruments developed from this

approach have arisen from clinical research in psychopathology. A multitude of

self-report measures have been developed to address the various domains of

psychopathology, mood and affect, psychological adjustment, and social

competence. In a review by Piotrowski and Lubin (1990), seven out of ten of the

most frequently used scales in health psychology were reported to be

psychological symptom inventories and scales that reflect mood and affect.

These instruments are self-report instruments that are used most prominently as

presumptive measures of stress. Most of these instruments are

multidimensional, reflecting the multitude of symptom complexes and myriad

dysphoric emotions typically invoked to define stress. The *Minnesota Multiphasic*

Personality Inventory (MMPI) (Hathaway & McKinley, 1940) is one of the best-

known multidimensional psychological tests and has been regarded as pivotal in

the development of personality research over the past 50 years. A second

popular multidimensional self-report instrument is the *SCL-90-R* (Derogatis et al.,

1973) and is designed to assess symptomatic psychological distress. The SCL-

90-R reflects psychological distress in nine primary symptom dimensions:

- Somatization (SOM),

- Obsessive-compulsive (OBS),

- Interpersonal sensitivity (INT),

- Depression (DEP,

- Anxiety (ANX),

- Hostility (HOS),

- Phobic anxiety (PHOB),

- Paranoid ideation (PAR), and

- Psychoticism (PSY).

Although most self-report instruments from the response-oriented perspective of stress are multidimensional, specific syndromes, particularly those that have become synonymous with definitions of stress such as anxiety, have fostered dedicated unidimensional instruments. Examples of popular unidimensional scales include the *Beck Depression Inventory* (BDI), the *State-Trait Anxiety Inventory* (STAI), and the *Center for Epidemiological Studies Depression Scale* (CES-D). The BDI (Beck et al., 1961) is a unidimensional symptom inventory focused on the measuring the behavioral manifestations that define the construct of depression. The STAI (Spielberger et al., 1970) is a self-report symptom-mood inventory comprised of two unidimensional scales intended to provide an operational distinction between anxiety as a transient emotional experience and anxiety as an enduring personality characteristic. The CES-D (Radloff, 1977) is a brief scale measuring depression by assessing mood and level of overall functioning during the most recent week (Derogatis & Coons, 1993).

Along with the response-oriented instruments based on psychological symptoms, affect and mood scales have been employed to operationalize stress through this approach. These scales are typically collections of adjectives depicting various mood states that are often selected on the basis of factor-analytic studies. Three popular affect and mood scales are:

1. *Profile of Mood States* (POMS) (McNair et al., 1971) – reflects six primary mood states including tension-anxiety, depression-dejection, confusion, anger-hostility, vigor, and fatigue.

2. *Affects Balance Scale* (ABS) (Derogatis, 1975) – incorporates positive and negative affect measuring current emotional status, general well-being, or treatment-induced change (Derogatis & Coons, 1993).

3. *Positive and Negative Affect Schedule* (PANAS) (Watson et al., 1988) – designed to express the idea that both positive and negative effects must be measured to achieve a valid estimate of general well-being.

The interactional theories of stress posit that cognitive, perceptual, personality, and other characteristics inherent in the individual mediate the response to stress. Instruments developed from these theoretical approaches have been based on individual and family interactionist models and represent newer measures of stress. The *Jenkins Activity Survey* (JAS) (Jenkins et al., 1967) is a self-report screening instrument developed to measure a specific pattern of behavior thought to have a high association with proneness to coronary disease known as the *type A* behavior pattern. The *Derogatis Stress Profile* (DPS) (Derogatis, 1987), an interactional stress measure, reflects stimulus, response, and interactional elements derived directly from stress theory. This instrument was conceived to be a truly interactional measure of stress that provides information on the level of environmental stress the

individual is subjected to, the impact of stressors, and the level of conscious

emotional distress the individual is experiencing as a result of the stressor-

mediator interaction. Although interactional theories of stress have guided the

development of relatively few self-report instruments, other instruments include:

- *Ways of Coping Checklist* (WCCL) (Folkman & Lazarus, 1980, 1985) –
  designed to identify strategies individuals use to deal with the demands
  of a stressful event,

- *Family Inventory of Life Events and Change* (FILE) (McCubbin et al.,
  1981) – assessing family reactions to the accumulation of demands
  associated with stressful events and changes,

- *Family Crisis Oriented Personal Evaluation Scales* (F-COPES)
  (McCubbin et al., 1981) – evaluating the cognitive and behavioral
  coping strategies families use when faced with stressful events, and

- *Coping Health Inventory for Parents* (CHIP) (McCubbin et al., 1983) –
  designed to examine the coping strategies used by parents who have
  a chronically ill child (Derogatis & Coons, 1993).

In addition to these instruments and methods used to capture information

about stress with any given theoretical approach, one reviewing the research

literature on stress is likely to encounter references to autonomic responses.

These physiological indices of stress, in fact, are rooted in the work conducted by

Selye and other researchers that culminated in such a vast and varied field of

research. Physiological measures of stress are just as varied as the theoretical

conceptualizations and definitions of stress. Psychophysiology represents a

common interest of psychologists, physicians, and biomedical engineers in the analysis of mind-body interactions through the measurement of bioelectric signals. Therefore, this field of research represents a heterogeneity of interests largely defined by its methods. Although the sympathetic and parasympathetic divisions of the autonomic nervous system consists of all the nerves that innervate the smooth muscles of the viscera, the endocrine glands, the heart, and the blood vessels, psychophysiological attention primarily focuses on cardiovascular measures and on the measurement of palmar sweat gland secretions. Electrodermal responses refer to skin conductance. Measurement of these responses has become a common practice in psychophysiological assessment. Although the exact relationship between psychological phenomena and electrodermal responses is still not entirely understood, its popularity as an index of stress lies in the fact that the innervation of the sweat glands is exclusively known to evoke anxiety and stress reactions. Because many technical considerations are necessary for the proper measurement of electrodermal activity, recommended standards have been established by the Society for Psychophysiological Research. Other popular psychophysiological measures evaluate cardiovascular activity and include the following measures:

- Electrocardiography – measuring the electrical activity associated with the contraction of the cardiac muscle,
- Impedance Cardiography – used to measure the impedance of the thorax to a high frequency low level alternating current going from the

neck to the abdomen through a band electrodes wrapped around the

abdomen, and

- Blood Pressure – measuring the pressure within the arteries during

   each cardiac cycle.

In addition to these psychophysiological measures, fundamental biological

markers are also used as indices of stress. These include, but are not limited to,

adrenaline excretion, plasma triglycerides, serum iron levels, neurotransmitters,

corticosteroids, and neuropeptides. While these indices are arguably more

objective measures of stress, criticism of these biological makers as indices is

that they lack sufficient specificity (Fowles et al., 1981; Derogatis & Coons, 1993;

Katkin et al., 1993; Thoits, 1983).

Stress Research

Since the publication of the study "Research on Stress in Health Disease"

in 1979, while stress research has still remained mainly concerned with

maladjustment or the negative consequences associated with stressors, interest

in successful coping strategies has become a field of interest and study among

researchers. The domain of stress research now puts heavy emphasis on

coping and coping mechanisms. Interest in coping strategies and individual

predispositions, as well as the efficacy of teaching coping skills, has grown

substantially. Goldberger and Breznitz (1993) assert that this new emphasis in

stress research demonstrates an optimistic bias. They maintain that practices

related to coping skills rest on the assumption that given the right tools, an

individual can cope effectively with most sources of stress. Another indication of

an optimistic bias in the stress research and literature is the attention given to the importance of the idea of control. Researchers assert that an internal locus of control is preferable to an external one and argue that self-control can be used effectively to combat the potentially harmful effects of stress (Goldberger & Breznitz, 1993). Based on this optimistic bias now found in the stress research and literature, Breznitz and Goldberger (1993) predict that stress research and theory are about to undergo a major change in emphasis. As opposed to investigating the negative impacts of stressors, Breznitz and Goldberger contend that illness related impacts of stress will give way to consideration of stress as a force conducive to health. Furthermore, they assert that this upsurge of interest in the positive effects of stress will significantly increase the relevance of the research field of stress (Goldberger & Breznitz, 1993).

While early investigations conceptualized stress as a nonspecific response of the body to any demand, it now encompasses experiences as well as the body's response to these experiences. In current research, the term stress generally refers to challenges, real or implied, to the homeostatic regulatory processes of the organism. Therefore, stimuli such as heat or cold and physical trauma are direct assaults on the homeostasis of an organism and emotions represent internal states that threaten the internal stability of a body. Current research has moved past investigations focusing on stressors to investigations focusing on the stress response. Investigations of the stress response consist of a cascade of neural and hormonal events that may have short term or long term consequences on the brain and the body. Within this

view, a stressor is defined as an environmental event that is likely to cause a negative outcome such as disease and psychological stressors such as fear or anxiety involve perceived threats to a body's homeostasis and are likely to evoke psychosomatic reactions such as gastric ulcers or immunosuppression and involve changes in the neural and hormonal output. A primary research focus between stress and pathophysiological responses has been on the adrenal steroids as agents that mediate adaptation and damage as a result of stress. Other research has focused on the psychological and biological effects of stress on the immune system through neuroendocrine processes, while other research is demonstrating that in the stress response, a dissociation between the different endocrine systems often occurs (McEwen & Mendelson, 1993; Stein & Miller, 1993). In addition, psychoendocrinological stress responses are being examined in infertility research based on the evidence that prolactin (PRL) and cortisol concentrations appear to be important in fertility, (Demyttenaere et al., 1992). As this research continues to grow in the fields of neurochemistry, neurobiology, and neuroendocrinology, and the neurosciences in general, a new scientific paradigm that redefines the stress construct to include the complex relationships between developmental, psychosocial, and biological science may emerge and provide a more precise construct with more tangible, quantifiable entities in which to investigate the stress response (Derogatis & Coons, 1993).

The widespread interest in stress and the stress response can be seen through the establishment of a variety of professional organizations dedicated to this field of research. One such organization, The American Institute of Stress,

continues to report on the latest advancements in stress research and health related issues. This organization also sponsors the International Congress on Stress which was initiated in order to assemble leading authorities from all over the world to present cutting edge research advances and state of the art reviews (American Institute of Stress [AIS], 2003; Rosch, 2003). Other established professional organizations include the Stress and Anxiety Research Society (STAR) and the Center for the Study of Stress and Adaptation that are both multidisciplinary research centers. In addition to the medical interest in stress and the stress response, social scientists continue research in the field. Current popular research focuses on stress ecology, job or work related stress, and research on family stress and coping mechanisms. In addition, with national high stakes testing requirements for students nationally, educators have a continued interest in test and performance anxiety as well as how to mitigate these responses in order to provide accurate estimates of a student's achievement on these high stakes tests (Ball, 1995; Stress Research Center [SRC], 2003; Spielberger & Vagg, 1995).

Stress and Infertility

Generally, infertile couples have carefully examined their reasons for desiring a child. They identify many of the philosophical values that most take for granted such as links to the future, sources of pleasure, pride, and challenge, and meaning in life. For many couples seeking medical treatment for infertility, parenthood is an important life goal that satisfies the need to develop as an adult and to demonstrate independence and creativity (Anderson & Alesi, 1997).

According to Savage (1989), the psychological importance of parenthood is that

it biologically preserves the continuation of the species and the child, in part

completes the parents. The inability to conceive a biological child is not only an

interference in the progression of adult development, but may also be a

frustration of a deep need to reproduce one's self and create the next generation.

While medical treatment of infertility can lead to resolution through the

conception and birth of a biological child, for many couples, infertility treatment

will not be successful. Therefore, the couples' task becomes one of resolving

this interference in this important life goal on a psychological and emotional level

(Mahlstedt & Wood, 1995; Anderson & Alesi, 1997; Domar & Seibel, 1997).

Infertile couples experience a variety of emotions and reactions. These

emotions and reactions can vary greatly across infertile individuals and couples

and may be greatly effected by a number of factors including, but not limited to,

the individual's or couple's support system, religious belief, and financial stability.

Ambiguity revolving around the diagnosis and not knowing what is going to

happen next along with being forced to change daily routines and life plans are

central themes to the emotional experiences of many infertile couples who are

trying to define and resolve the dilemmas created by their infertility. Infertile

couples have to develop ways in which to cope with the uncertainty that infertility

creates as well as make decisions about treatment that will be in the best interest

for their relationship and their hoped-for children. While infertility patients

struggle with the uncertainty surrounding their infertility and eventual treatment

outcomes, physicians specializing in reproductive endocrinology must also deal

with the frustrations of not knowing what will happen next or how they should

respond to their patients' needs for answers to the psychosocial questions that

they pose. It is fair to conclude that all participants in assisted reproductive

technology have hope that medical goals will be achieved and desire a happy

ending for all involved even though there is uncertainty regarding the duration or

ramifications of the treatment decisions (Menning, 1980; Mahlstedt & Wood,

1995; Anderson & Alesi, 1997; Domar & Seibel, 1997).

     Many studies investigating the emotional experiences of couples

experiencing infertility are anecdotal, reporting the comments and descriptions of

the experience of couples interviewed. Perhaps one of the most compelling

comments illustrating the poignancy of the ambiguity and emotional distress

surrounding the experience of infertility follows:

     "When you absolutely cannot have children, it's called sterility.

     When it seems to be taking an awfully long time but you still have

     hope, it's called infertility. Infertility is worse" (OTA, 1988)*.*

Creating a "happy ending" may be viewed as the resolution of the emotional

dilemmas created by infertility, as well as making good decisions about infertility

treatment options.

     The impact of infertility and the resulting stress emanating from

infertility diagnosis and treatment have been well documented in the

research literature (Domar & Seibel, 1997; Greil, 1997; Schneider, 2000).

The stress of infertility on individuals and couples can have negative

effects on physical and mental health, the couples' relationship, career,

finances, as well as social and family networks (Domar, 1997; Domar &

Seibel, 1997; Schneider, 2000). Individuals and couples experiencing

infertility treatment can feel emotionally depleted, isolated from others, and

vulnerable to experiencing a series of losses and chronic stress

(Mahlstedt, 1985; Schneider, 2000).

<div align="center">*Emotional Aspects of Infertility*</div>

The diagnosis and treatment of infertility may have a profound impact on

the lives of those couples. The processes of diagnosis and treatment may lead

to conflict in the most stable of relationships or exacerbate existing problems

between spouses. While this conflict has been shown to be greater when the

treatment process is prolonged or unsuccessful, the emotional distress begins to

develop when a couple realizes that their plans to conceive and to begin their

family are not coming to fruition. Immediate consequences of infertility include

worrying, having doubts about the realization of their family goals, and frustration.

Daily routines change significantly for infertile couples after medical treatment

begins. These changes can take an exacting toll on the couples' quality of life,

affecting the emotional, social, physical, occupational, intellectual, and even

spiritual well being of those involved (Seibel & Taymor, 1982; Cooper, 1993;

Mahlstedt & Wood, 1995; Anderson & Alesi, 1997).

According to Menning (1980), infertility is a process that consists of

several different emotional phases beginning with a phase of initial shock leading

to denial, depression, and eventually to resolution and acceptance of the

infertility. The first phase that couples typically experience when diagnosed with

<div align="center">91</div>

an infertility problem is one of shock and surprise. Because many couples carefully plan when to begin their family, the inability to conceive is generally unexpected. Most assume that they will have no difficulty in conceiving and reproducing. In addition, society tends to support controlling fertility until children are desired. Therefore, little preparation exists for the possibility of infertility. Following the initial shock of an infertility diagnosis, couples typically proceed through a phase of denial. Denial is especially characteristic for couples whose diagnostic evaluations reveal an absolute and untreatable problem (Menning, 1980; Domar & Seibel, 1997).

While most adults feel that they have some control over the decisions affecting their lifestyle, for those couples seeking treatment for infertility, the treatments superimpose an agenda that severely compromises their ability to either enjoy the present or plan for the future. Couples struggling with infertility tend to be highly motivated towards parenting and readily forego many other positive aspects of life in pursuit of conceiving and having a child. In addition, couples seeking infertility treatment are usually self-directed, in control of their lives, and have committed to the ethic that hard work leads to success. For these individuals, infertility can be a devastating experience. Regardless of the financial burden felt by infertility treatment, the lack of children makes everything that they work for seem meaningless to some infertile couples. These feelings lead to the next emotional phase of anger that couples generally encounter through the infertility process. Even though an infertile couple may attempt to control their infertility by seeking diagnostic testing and therapeutic procedures,

powerlessness is a major feature of the infertility experience because only a

small percentage of those who undergo treatment for infertility achieve

pregnancy. The reality is that the outcome of infertility treatment is beyond the

couple's and physician's control. The unanswerable question "Why?" plagues

infertile couples while their anger is fueled by the conflicting demands of work

responsibilities and infertility treatment as well as any perceived insensitivity of

friends, family, and even their physicians. Independence and flexibility that were

once in the control of the couple are lost as their lives begin to revolve around

their physician's plans for conception including medications, injections,

ultrasound examinations, and surgeries. The couples' attention becomes

focused on conceiving, and other goals, priorities, and needs are neglected. The

focus on medical treatments and any subsequent failures can have a negative

impact on their self-esteem, health, relationships, security, and even their

ambitions. Each month of treatment contains hope for two weeks and despair for

two weeks with each failure to conceive, creating a roller coaster of emotion with

hope on the upside and depression, anger, and guilt on the downside. In

addition to the uncertainty of infertility and treatment outcomes, given the fact

that couples must surrender much of their control over their bodies as well as

their plans for a family, anger is a predictable response. According to Menning

(1980), even the best relationship between the physician and the patient does

not alleviate all of the frustration, helplessness, and embarrassment that may be

experienced by the couple. The anger experienced by couples may be rational,

focusing on real and correctly perceived insults, such as societal pressure to

reproduce, or the pain and inconvenience of infertility tests and treatments.

However, the anger experienced by couples may also be irrational where anger

is projected against others such as abortion-rights advocates, people who "breed

like rabbits", or those who neglect, abuse, or mistreat children. In addition,

infertility patients may project their anger onto those who they feel have control

over them such as their physician or nurses providing the infertility treatment.

According to Menning (1980), this irrational anger is usually a front for intense

pain and grief that cannot yet be acknowledged by the person (Menning, 1980;

Seibel & Taymor, 1982; Imeson & McMurray, 1996; Domar & Seibel, 1997;

Anderson & Alesi, 1997).

Feelings of guilt contribute to the secrecy that so often surrounds infertility.

Infertility patients often feel guilty about their inability to conceive or impregnate,

for letting down their spouse, families, and other loved ones, as well as for the

emotional responses they have to the infertility diagnosis and treatment.

Infertility patients often feel responsible for their infertility. Many couples view

infertility as a "punishment" and search for a reason on which to blame their

infertility. Couples have identified a variety of reasons for which they attribute the

punishment of infertility including premarital sex, the use of birth control, a history

of abortion or impregnation, venereal disease, extramarital affairs, masturbation,

homosexual thoughts or acts, and even sexual pleasure. Those patients who

attribute their infertility to a particular deed or action in their history will typically

go to great lengths to atone for these "sins". Atoning may take many forms from

religious acts to personal denial or to working in painful areas such as counseling

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unwed mothers. Most often, these feelings of guilt are generally resolved by the

acceptance that people cannot control every aspect of their lives and that there is

no relationship between fertility and worthiness (Menning, 1980; Mahlstedt &

Wood, 1995; Anderson & Alesi, 1997; Domar & Seibel, 1997).

Depression is the emotional state that permeates all other experiences

and is common among couples during infertility evaluation and treatment. Even

when the infertile couple has reason to be optimistic about the success of

treatment leading to pregnancy, this hope is usually coupled with feelings of

depression that generally intensifies with each failure. Infertility involves

experiencing a series of losses which have been found to be of greatest

importance in the etiology of depression. Some of the losses felt by the infertile

couple are resolved by medical technology or through other alternatives such as

adoption or the use of donor gametes. One important contributing factor to

depression is the loss of a relationship with an emotionally important person due

to death, divorce, the waning of affection, or separation. Because infertility is

often a difficult subject for most to discuss due to the very personal and

inherently sexual nature of it, couples may tend to keep their infertility secret from

others. This secrecy cuts couples off from potential sources of support and

comfort, which leads to feelings of isolation. Without children, infertile couples

are inherently excluded from important social networks, social events, and

parenting experiences. The social isolation experienced by infertile couples can

have a major impact on their lives. In extreme situations, couples faced with

infertility may be so sensitive to issues of pregnancy or little children that they

withdraw from all social or work related situations that might lead to such a

contact. While the isolation of couples experiencing infertility from others in

family, work, or social environments may be difficult, even more devastating is

isolation from their spouse. This isolation generally results from a breakdown in

communication and erodes the family dynamic leading to increased marital

stress. The partners themselves may experience a loss of closeness simply

because the infertility diagnosis and treatment affects them differently or because

they cope differently. For women, the potential loss of fertility is generally more

threatening than for men. Typically, women are more emotionally expressive,

willing to discuss their anxiety and depression with their spouse, who may often

feel powerless to help or unsure of how to respond. Men, however, typically

contain their emotions, not only to sustain the stoicism that they feel is expected

of them, but also out of a sense of responsibility to be the stable and calming

force in the relationship (Sherrod, 1995; Schneider, 2000). Unfortunately,

women may misunderstand this basic difference, often leaving women to feel

unloved or abandoned when their husbands do not experience the same kinds of

feelings of loss or emotional pain (Menning, 1980; Cooper, 1993; Mahlstedt &

Wood, 1995; Imeson & McMurray, 1996; Domar & Seibel, 1997).

Another important etiological factor contributing to depression in adulthood

is the loss of health, important body functions, or acceptable self-image or body

image. Most couples seeking medical treatment for infertility are in good health

and have positive body and self-images. Diagnostic procedures and infertility

treatments can assault positive images of oneself. Patients relinquish their

bodies over to medications that may have severe or debilitating side effects.

Their sexual spontaneity all but disappears and is replaced instead by sexual

schedules with the frequency and timing of intercourse prescribed by their

physician. Additionally, the amount of time spent in physician appointments or in

decisions to proceed with surgical treatment options may threaten the individual's

sense of health. Individuals accustomed to feeling in control of their health,

bodies, and lives may suddenly feel that they are defective because they are

unable to perform the most fundamental task of life, that of reproduction

(Mahlstedt & Wood, 1995; Anderson & Alesi, 1997).

    In addition to the loss of a relationship and sense of health, the loss of

status or prestige, self-esteem, self-confidence, and security all contribute to

feelings of depression. The experiences of infertility can invoke feelings of loss

of these types in varying degrees among couples. Because society places great

value on parenthood, infertility can lead to the perception of loss of status or

prestige in the eyes of others. The expectation that infertile couples feel to have

children can leave infertile couples feeling different, abnormal or less acceptable.

Because they are unable to meet societal expectations to conceive and raise

children, they suffer a social stigma attached to the infertility (Cooper, 1993;

Mahlstedt & Wood, 1995, Domar & Seibel, 1997).

    Some infertile individuals feel that their sexual identities are inextricably

linked to reproduction. These feelings are reinforced socially through notions

that masculinity, virility, fertility, and potency are equated. Infertile men often

report feelings of emasculation which deals a considerable blow to their sexual

self-image. Some infertile men with no history of sexual dysfunction or inadequacy become impotent for a period of time after the discovery of male factor infertility. Among women, the idea of motherhood is usually linked to their adult identity. Infertility may cause feelings of inadequacy and many women feel that they are unlovable, unfeminine, damaged, or defective. For both men and women, sexual functions may become synonymous with failure, highlighting the failure to conceive and, therefore, the failure to be an adequate man or woman. These negative emotions deepen as infertility continues and are often generalized so that their global self-esteem is affected. The loss of self-esteem or pride generally leads to a sense of failure. Infertility is the inability to conceive after one year of unprotected intercourse or the inability to carry a pregnancy to a live birth. By definition, infertility is a description of failure. Although the emotional responses that accompany infertility can vary greatly among individuals, they are generally very strong and usually come as a surprise to many infertile couples. When an individual or couple experiences a strong and unexpected emotional response, it is common for self-esteem to erode as they become so poignantly aware of the extent to which emotions appear to rule their lives as never before. In addition, this damage to self-esteem is not easily repaired and usually affects the individual's deepest sense of self, including their feelings about their own masculinity, femininity, and sexuality (Cooper, 1993; Mahlstedt & Wood, 1995; Anderson & Alesi, 1997; Domar & Seibel, 1997).

The time and expense involved in the treatment of infertility can result in the loss of occupational, financial, social, and cultural security. Occupational and

financial security is especially vulnerable when infertility is prolonged, requiring

frequent visits to the physician, expensive medications, and costly diagnostic or

surgical procedures that often interfere with work schedules. Because most

insurance companies cover only part, if any at all, of infertility diagnosis and

treatment procedures, most couples are burdened with the financial strains that

infertility creates. Job performance as well as job security and relationships with

coworkers can be jeopardized. Social and cultural security is endangered if the

infertile couple experiences feelings of isolation from others whose lives center to

a large degree on their children (Mahlstedt & Wood, 1995; Domar & Seibel,

1997).

        Once all hope for achieving pregnancy and a live birth is abandoned, the

most compelling emotional reaction to infertility experienced by many couples is

grief. However, the grief experienced by couples as a result of infertility is unlike

any other grief experience. While grief usually follows the loss of something or

someone important to an individual, the grief experienced by an individual

resulting from infertility is based on something intangible. It revolves around the

loss of a potential, not an actual life. For many couples, infertility is the loss of a

dream or the hope of fulfilling an important fantasy or life goal. These infertile

couples yearn for the child who may never be and mourn for the child who never

was. To these infertile couples, this loss is as a real as if the child had been

born, lived, and died. Infertility that is conclusive with no potential of conceiving

or having biological children represents losses of many types. First, it the loss of

one's fertility and all that it means in relation to an individual's sexuality. In

addition, it is a loss of the pregnancy experiences itself. Menning (1980) reports

the loss experienced by one infertility patient:

> *"Death. Death of a lot of things. It is the end of the Bowes family*
>
> *and the Bowes family name. It dies with us because of me. My*
>
> *husband is the last of the male children in his family. Death before*
>
> *life… before we even knew our child, because he never existed.*
>
> *The hardest part of this kind of death is that it is the death of a*
>
> *dream. There are no solid memories, no pictures, no things to*
>
> *remember. You can't even remember your child's blonde hair, or*
>
> *brown eyes, or his favorite toys or the way he laughed, or the way it*
>
> *felt to be pregnant with him. He never existed."*

Although society has elaborate rituals to comfort the bereaved in the death of a

loved one, none of these rituals are available for those experiencing the grief of

infertility. In addition, because there is no tangible loss for all to see, family and

friends may never even know of the grief experienced by couples, leaving these

couples to grieve for their loss alone. Generally, infertile couples feel wounded

and those wounds of hurt and mourning are often reopened. Children remind

them that they are infertile. Pregnant women remind them of the pregnancy that

they were never able to experience. Television commercials featuring toddlers,

birth announcements from friends, and families with children in Sunday worship

services can all contribute to the insult and grief felt by infertile couples (Menning,

1980; Mahlstedt & Wood, 1995; Anderson & Alesi, 1997).

The final emotional stage that infertile couples experience is the stage of resolution. When an infertile couple finally reaches the stage of resolution and acceptance, plans for the future can be made, building a way around the obstacle of infertility. Couples are ready to select alternative life plans including decisions about adoption with confidence. With the ambiguity of infertility past, couples are ready to once again exert control over their life plans and to proceed with their lives. Unfortunately, some infertile couples or individuals may never reach acceptance or resolution. For some the loss and the pain of infertility will be felt throughout their lives (Menning, 1980; Mahlstedt & Wood, 1995).

Conceptualization of Stress in Infertility Research

The emotional experiences of infertility have been conceptualized in a variety of frameworks (Schneider, 2000). During the 1940s and 1950s, both medical and psychiatric research literature contained several case reports of infertile men and women who sought psychiatric care for depression, obsessive-compulsive behavior, or neurosis. As a result, a theory of the psychological etiology of infertility known as the psychogenic morbidity model or psychogenic hypothesis evolved. The psychogenic model was clearly the dominant theory up through the mid-1980s (Bernstein, 1993; Greil, 1997). This theory postulated that female infertility, particularly those cases with unidentified organic causes, are caused by an unconscious resistance to motherhood on the part of the female. The theory asserts that males with idiopathic infertility exhibit extreme animosity and aggressiveness toward their wives, thereby preventing conception. As described by Rutherford et al. in 1966, the psychogenically infertile male is

typically from an above-average educational background, with a domineering mother who is sexually unsatisfied herself, the experience of a childhood threat to have love withdrawn for being "naughty" such as exhibiting any sexual behavior, lack of sexual activity before marriage, and conflict within marriage between sexual desire and fear of offending their partner (Bernstein, 1993; Greil, 1997).

One major contributing factor in the development of the psychogenic hypothesis is that during this time, reproductive endocrinology was in its infancy. While approximately 50% of infertility patients received a diagnosis identifying the etiology of their infertility, the remaining 50% of patients were diagnosed with idiopathic infertility. Therefore, psychiatrists incorrectly concluded that in patients diagnosed with infertility of unknown origin, the etiology of the infertility must be psychogenic. In addition to the lack of understanding of reproduction as well as the etiology of infertility, the foundation for the development of the psychogenic theory can be found in the work conducted by Helena Deutsch during 1945. In her writing, *The Psychology of Women,* Deutsch identified five types of women who she believed caused their own infertility: (1) the infantile, dependent woman looking for attention, (2) the woman whose motherliness is "consumed in a fire or erotic love…or devotion to an ideology", (3) the woman who exhausts her motherliness on her husband and knows that he would not welcome the competition of a child, (4) the masculine, aggressive woman who refuses to accept her properly passive role in society, and (5) the emotionally disturbed woman who fears the additional burdens a child would create. At the conclusion

of the 1950s, these five types of women had become the standard for the

examination of emotional issues in infertility (Deutsch, 1945; Rutherford et al.,

1966; Bernstein, 1993).

During the 1960s and 1970s, a new formulation and insight into the

theories of the role of stress on infertility began to develop. Psychologists, social

workers, nurses, infertility specialists, and psychiatrists began to research the

relationship between emotional distress and infertility. This effort was greatly

advanced with the application of several neuropsychological tests including the

Minnesota Multiphasic Personality Inventory (MMPI), Rorschach, Neuroticism

Scale, and the Thematic Apperception Test (TAT). Results of this research

indicated that there were no differences in test performance between the infertile

couple and the fertile population. Research also demonstrated that the distress

experienced by couples related to infertility was not sufficient to manifest

psychiatric symptomatology. In addition, the treatment of psychiatric symptoms

among infertility patients experiencing distress and anxiety did not change their

infertility status. However, psychiatric treatment was shown to improve patients'

sense of well being. These studies led to mounting evidence refuting the

psychogenic hypothesis (Bernstein, 1993).

Some researchers have begun to modify the psychogenic model with

another theory based on the idea that stress causes infertility. The importance of

the relationship between stress and health as well as the suspicion that stress

may be causally linked to infertility is not unreasonable and supports the

modifications of the psychogenic model. However, this modified view has not

become popular with researchers, counselors, or infertile couples themselves

because the psychogenic hypothesis is generally regarded as a mechanism for

minimizing the reality of the distress associated with infertility and also as a

means for casting blame on infertility patients for their own suffering. To infertility

patients, as well as to those who sympathize with them, the psychogenic

hypothesis seems like a reiteration in scholarly guise of well-intentioned advice

such as "Relax" or "Take a vacation and you'll get pregnant in no time" (Greil,

1997). While most researchers today reject the psychogenic hypothesis, some

attempts have been made to revive this theory as conceptual framework for

investigating the relationship between stress and infertility. According to Astor

and Pawson (1986), personality measures do not adequately portray

unconscious motivation. Therefore, they conclude that these measures do not

contest the psychogenic hypothesis (Greil, 1997).

Barbara Eck Menning is recognized as instrumental in the development of

a cognitive construct for describing the emotional aspects of infertility for couples,

how couples process the diagnosis, and how these couples proceed toward

resolution of the psychological distress that couples experience as a result of

infertility. The crisis model, which was first described by Kubler-Ross in 1980,

was subsequently refined through the work conducted by Menning and others in

order to be applied appropriately to infertility. Loss is a central theme in the crisis

model, incorporating the stages of grief. The losses described by Mahlstedt and

Wood (1995) include: the loss of a relationship or potential relationship; the loss

of one's health, the loss of status or prestige, the loss of self-esteem, self-

confidence, or security; the loss of a fantasy or hope of fulfilling an important fantasy; and the loss of something or someone of great symbolic value. This model recognizes infertility as a disruption in the normal equilibrium, which taxes couples' existing resources and threatens life goals, and recognizes that infertility may also awaken unresolved psychological problems. This conceptualization of infertility acknowledges the emotional roller coaster couples experience throughout the process. In addition, this model acknowledges that couples may experience a variety of emotions and behaviors at different times and in a different sequence from other infertility patients. These emotions include surprise, guilt, denial, anger, a feeling of isolation, grief, and finally, a sense of resolution or acceptance. In addition, it is recognized that infertility, unlike other life crises, is not bound within a given time frame. Infertility is viewed as processional, encompassing a series of related crisis events before resolution is reached. Therefore, infertility is conceptualized as both a major life event as well as a prolonged crisis with a series of daily hassles that may potentially impact all aspects of the infertile couple's life (Blenner, 1990; Mahlstedt & Wood, 1995; Imeson & McMurray, 1996; Schneider, 2000). Similar to any other life crisis, resolution could either be maladaptive change or an increase in maturity and emotional strength. The development of this cognitive construct of infertility led physicians, for the first time, to consider infertility patients' emotional needs simultaneously with their physical and medical needs. It was at this time that the concept of infertility physicians joining with appropriate mental health professionals began to evolve (Bernstein, 1993).

In addition to the work conducted by Menning, several other researchers have been instrumental in the expansion of the description of the emotional experiences of couples dealing with infertility and the refinement of the crisis model as it applies to infertility. Research has expanded the literature to include the intrapsychic conflicts that infertility arouses, the effect of infertility on marital relationships, gender differences in the response to infertility, common coping strategies employed by infertile women, and the aspects of loss of control as well as the negative effects infertility has on self-image and generational identity (Bernstein, 1993).

The Reproduction Filtering Model (sometimes referred to as the adaptive reproductive failure model) has also been developed by evolutionary biologists to explain why the rates of reproductive failure are so high in mammals. Adherents of this theoretical conceptualization of the relationship between stress and infertility argue that the high cost of reproduction in terms of time, energy, and risk has naturally selected for physiological mechanisms that terminate reproductive attempts when the likelihood of reproducing viable offspring is low. Therefore, this response conserves time and energy for reproduction that is most likely to succeed. This model implies that the reproductive system has evolved a high physiological responsiveness to environmental change. The application of this model to humans is based on the argument for the likely effectiveness of acute and long-term environmental therapy such as diet, stress reduction, or psychosocial therapies as treatment for some forms of reproductive failure (Wasser et al., 1993).

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The Stress and Infertility Relationship

Research has established that many endocrine systems respond to stress. As originally proposed by Selye, stress is a nonspecific response of the body to any demand. This paradigm asserts that any kind of stressor provokes the same kind of response in every individual. This response was believed to be dependent only upon the time a stressor could influence an organism. However, research over the past several decades has demonstrated that different stressors, whether they be physical or psychological, can result in different responses by a system and the psychological mechanism of anticipation determines the effect of the stressor. Furthermore, evidence suggests that individuals may respond differently to the same stressor. It has also been demonstrated that in the stress response, there can be dissociation between emotional and endocrine states. In addition, research has found that in the stress response, a dissociation between the different endocrine systems often occurs suggesting that different parts of the endocrinological stress response are linked to specific psychological stressors or to the effectiveness of psychological functioning such as cortisol to ineffectiveness of defenses (Selye, 1956; Mason, 1975; Ellertsen et al., 1978; Weinberger et al., 1979; Vaernes et al., 1982; Allen et al., 1985; Demyttenaere et al., 1989).

The importance of coping mechanisms is also established by the scope of the research dedicated to the role coping mechanisms play in psychological functioning. Current stress and coping research focuses primarily on the stress-reducing effects of coping skills. Although coping may lead to a reduction in the

stress experienced by an individual, the execution of coping skill or strategy may serve as a source of stress and therefore may activate some dimensions of the stress response (Demyttenaere et al., 1991).

The Role of Psychoeducational Interventions in Infertility

Cognitive therapy is increasingly being accepted as an effective treatment option for depression (Domar et al., 2000). Several studies with cancer patients combined support with cognitive-behavioral techniques. The benefits of this educational model included decreased psychological distress, longer life span, and decreased mortality (Helgeson & Cohen, 1996; Domar et al., 2000). Cognitive-behavioral approaches have been shown through a multitude of studies and investigations to be effective in reducing symptoms of depression and decreasing health costs for patients with a wide variety of conditions including cardiac, abdominal, orthopedic, dental surgery, and invasive medical procedures (Mandle et al., 1996; Domar et al., 2000). Another study of patients with multiple sclerosis emphasized coping-skills training. This study demonstrated greater advantages in well-being and coping for the patients receiving the coping skills training than for those who participated in only a peer telephone support group.

Several principals form the foundation of cognitive behavioral treatment:

- Unconditional regard for self and others involves the acknowledgement and acceptance of an individual's strengths and limitations. While all humans are predisposed to self-rating and rating of others, the objective in cognitive behavioral therapy is to

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minimize the rating and judgment of self and others and to control

the manner in which it occurs (Ellis, 1977; Granvold, 1994).

- The continuity assumption is the presumption that covert behaviors

  are subject to the same rules of learning as overt behaviors.

  Therefore, cognitions can be taught like overt behavior is taught

  through techniques such as modeling, coaching, rehearsing, and a

  variety of other methods. Complex cognitive transactions can be

  broken down into smaller "chunks" and learned incrementally.

  Cognitions can variably function as a stimulus, response, or

  consequence and can be strengthened, weakened, or extinguished

  through reinforcement (Mahoney, 1974; Granvold, 1994).

- Conditioning is a term referring to the individual learning history and

  associated attitudes that influence an individual's process of

  anticipation, selection and decision-making in a given situation

  (Schindler & Vollmer, 1984; Granvold, 1994).

- Self-responsibility for one's own emotional disturbance and

  maladaptive behavior.

- Questioning and the Socratic Method to promote desired changes

  (Beck & Emery, 1985; Granvold, 1994)

Couples participating in cognitive-behavioral therapy are typically introduced to a

wide variety of techniques, including relaxation-response training, cognitive

restructuring, emotional expression, and nutrition and exercise education

relevant to infertility (Domar et al., 1990, 2000; Connolly et all, 1993).

Based on mounting evidence, reproductive endocrinologists have begun to acknowledge the importance of addressing the emotional needs of their patients simultaneously with their physical and medical needs. However, several factors have limited the acceptance and application of programs aimed at educating patients about stress-reduction therapies as compared to the rapidly expansion of the biomedical technology:

1. Few studies have empirically challenged the belief of physicians that stress is not causally linked with infertility to a significant degree;

2. Psychosocial problems tend to be more difficult for patients to acknowledge than biological problems,

3. Psychosocial therapy, patient education programs, and social support networks are relatively more time consuming and require considerably more effort on the part of the patient as compared to the biomedical treatments, and

4. Reproductive endocrinologists are not trained to diagnose psychological problems or to provide the therapies beneficial to mediate the effects of psychosocial stress.

The combination of these factors has led reproductive endocrinologists to rely primarily on biomedical treatments for infertility in this highly competitive field of practice. Unfortunately, a purely biotechnological approach may be successful in treating only the physiologic symptoms of infertility patients, without eliminating the stressors that triggered or accompany the symptoms. However, biomedical

treatment for infertility along with treatment for psychosocial stress could, arguably, markedly improve overall reproduction outcomes (Wasser et al., 1999).

Based on the mounting evidence about the stress of infertility and infertility treatment, some investigators have suggested that infertility treatment programs should incorporate a psychological treatment component. As early as 1959, acute psychological supports for infertile couples as an adjunct to medical treatment can be found. Recently, national organizations such as Resolve, Inc. in the United States and the National Association for the Childless in the UK offering referral support groups and infertility counseling have been established. These programs can be provided to patients in a variety of ways including traditional psychotherapy, group therapy, and social support networks (Anderson & Alesi, 1997).

Traditional individual psychotherapy interventions typically focus on the similarities in psychological responses between infertility and grief counseling. Counseling is particularly beneficial to infertile couples at three times during the treatment cycle: 1) the beginning of an infertility evaluation, 2) when a psychiatric disorder is present, and 3) the termination of unsuccessful treatment. These interventions generally address the long-term adjustment to infertility as well as the acute reactions to failed treatment attempts. Two main approaches in traditional interventions are: brief support counseling and therapeutic counseling, each of which may be offered to the individual or to the couple. The main components of a brief support program include empathetic listening, patient education, and problem solving. Because infertility is a significant loss to

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couples, infertility patients often have a great need to talk about their experiences. The role of the counselor is to facilitate the expression of fears, hopes, disappointments, anger, and sadness. This free expression is designed to facilitate further communication between the couple and to increase their understanding and tolerance of each other. In addition to facilitating communication, infertility patients can derive benefit from education about common emotional reactions to infertility. Finally, traditional counseling approaches can help patients to conquer a range of problems. Everyday problems can become compounded by infertility. Patients often become overwhelmed with questions such as what to tell their employer about their frequent absences, how to respond to genuine questions about whether they have children, and how to preserve a relationship with a sister or friend who is pregnant. Systematically working out individual patient concerns and problems can help to reinstate a sense of control over their lives (Anderson & Alesi, 1997).

While brief support counseling programs are beneficial to patients experiencing acute distress related to their infertility diagnosis or treatment, the aim of most therapeutic counseling is to help patients reach resolution in terms of their infertility. The concept of resolution within the context of therapeutic counseling implies that it is possible for an infertile couple to reach a point where infertility is not associated with emotional distress. The goal for infertile couples in this approach is to accept and incorporate the pain of infertility into their life so that it loses the acute quality experienced in the earlier stages of diagnosis and

treatment. The duration of therapeutic counseling varies and can be spread over

many years (Anderson & Alesi, 1997).

Couples' approaches typically address the negative impact of infertility on

marital adjustment and sexual satisfaction. Couples' approaches use therapy as

a means of improving communication and interactions between the spouses.

Group therapy has been described as a valuable venue for couples experiencing

infertility because so many of them report feelings of isolation. While reading

material can be beneficial to infertility patients, one of the most powerful

experiences is through support groups. It is generally believed that patient

education through contact with others who are also infertile can restore a sense

of normality, and begin to break down feelings of isolation and helplessness.

Groups demonstrate that infertile couples are not alone. In addition, they can

share thoughts, problems, experiences, and concerns with others in similar

situations. Participants can also lend support to other members of the group,

which is often beneficial and rewarding. Group therapy can lead to improved

communication with physicians as patients become educated about special

needs and learn to express their frustrations about medical interventions and it is

a cost effective way to address infertility patient's emotional needs (Anderson &

Alesi, 1997; Domar & Seibel, 1997; McNaughton-Cassill, 2000).

Unfortunately, few studies address the provision of therapy for couples in

the midst of their infertility procedures or the use of group therapy approaches for

the treatment of such couples (Domar & Seibel, 1997; McNaughton-Cassill,

2000). However, the value of psychoeducational interventions for individuals

undergoing treatment for other devastating illnesses, such as cancer, has long been documented to minimize both adverse psychological and physiological side effects. Behavioral techniques including the relaxation response, stress management, nutrition, and exercise counseling have been widely successful when applied to a variety of medical and psychiatric symptoms. The first application of these programs to infertile women in a clinical setting was in 1987. In this program developed and implemented by Domar, Seibel, and Benson, infertile women were educated in a variety of ways to elicit the relaxation response, "mini" relaxation techniques, cognitive restructuring, nutrition and exercise counseling, and methods for dealing with negative emotions (Domar & Seibel, 1997).

The most common interventions to help couples cope with the stress of infertility in the United States include patient education and social networking through support groups. While the programs vary, some common elements among all of them include educational programs and emotional supports designed to alleviate symptoms of stress for individuals or couples experiencing infertility. One such program is the Mind/Body Program for Infertility. Based on research regarding the emotional aspects of infertility, the Mind/Body Program for Infertility was developed and implemented in September of 1987. The foundation of this program lies in the assumption that women who regularly elicit the relaxation response will demonstrate decreased levels of tension and anxiety leading to an increased rate of conception. The relaxation response has been described as an innate physiologic response that is the counterpart of the

physiological response to stress referred to as the fight-or-flight response. The

relaxation response is associated with a set of coordinated physiological changes

including a decrease in oxygen consumption, carbon dioxide elimination, heart

rate, respiratory rate, blood pressure, muscle tonus, and arterial blood lactate. In

addition, an integrated hypothalamic response appears to lead to a series of

physiologic changes that are consistent in the sympathetic nervous system

activity. The relaxation response can be induced through a wide variety of

activities including progressive muscle relaxation, diaphragmatic breathing,

meditation, repetitive prayer, mental imagery, exercise, or absorption in a

pleasant task. Furthermore, the several benefits of the relaxation response have

been documented including decrease in chronic pain, hypertension, preoperative

anxiety, ventricular arrhythmias, and anxiety. The Mind/Body Program for

Infertility, established at the Deaconess Hospital in collaboration with the Division

of Reproductive Endocrinology at Beth Israel Hospital, is a ten-week educational

program including relaxation-response training, stress management training,

exercise, nutrition, group support, couples' cognitive-behavioral training, and

developing self-empathy and compassion. While this training focuses primarily

on women participating in ART procedures, regardless of the etiology of the

infertility, husbands are invited to attend two of the ten sessions. The main topics

for the 10 sessions are as follow:

    1. An introduction to the physiology of stress, the relaxation response,

       and the relationship between stress and the reproductive system;

2. The use of diaphragmatic breathing and mini-relaxation-response exercises;

3. Cognitive restructuring and affirmation training;

4. Developing self-empathy and compassion;

5. Exercise and nutrition;

6. Mindfulness, specifically an increased awareness of sensations and perceptions;

7. Emotions;

8. Anger and forgiveness;

9. Yoga, exercise, and couples' cognitive-behavioral exercises; and

10. Review and follow-up information (Domar et al., 1990; Domar & Seibel, 1997).

This program follows a 10-week protocol designed to treat individuals experiencing any medical symptoms caused or aggravated by stress and is based on the elicitation of the relaxation response exercise. In addition to this program, cognitive behavioral therapy is also accepted as an effective treatment option for depression among infertility individuals and couples (Domar et al., 1990, 2000; Connolly et al., 1993).

Summary of Research Examining the Relationship Between Stress and Infertility

The psychological effect of infertility experienced both individually and as a marital couple has now been widely documented through the research literature. Because ART procedures such as IVF and ICSI are the most complex, expensive, and invasive forms of infertility treatment, and are generally

the final treatment option for many patients, much of the research focuses on infertility patients participating in these treatment programs. Depressive symptoms are common in infertility patients undergoing IVF. Using the Schedule for Affective Disorders and Schizophrenia, Bell (1981) found that 40% of infertile women had mild to moderate symptoms of depression while 7% presented severe symptoms of depression. Freeman et al. (1983) found that 16% of women preparing to participate in an IVF treatment cycle had scores of 70 or higher on one or more subscales of the MMPI. Likewise, Garner et al. (1984) found that depressive symptoms were present in 34% of infertile women prior to an IVF treatment cycle and in 64% of the participants after an unsuccessful IVF cycle. In a prospective, longitudinal study of 59 infertile women seeking treatment, 9% of the infertile participants met the criteria for a major depressive episode as compared to 3% of the participants in a control group (Downey et al., 1989). In addition, one-half of the infertile participants reported changes in their sexual functioning while 75% reported changes in their mood. Others studies have documented similar findings. Wright et al. (1989) found that infertile women were significantly more distressed than control participants on the majority of psychological parameters investigated. In one investigation conducted by Freeman et al. (1987), half of their sample of infertile couples described infertility as the most upsetting experience of their lives. In another study conducted by Mahlstedt et al. (1987), 80% of the sample of infertile couples reported that their experience of infertility was either stressful or extremely stressful. The acknowledgement that psychological distress is one outcome of infertility and

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infertility treatment has led many researchers and authors to advocate for the

provision of counseling as an essential component in ART repertoires (Mahlstedt

et al., 1987; Dennerstein & Morse, 1985; Connolly et al., 1993).

Accumulating evidence suggests that stress may influence the outcome of

infertility treatment. While results of these investigations have led to conflicting

conclusions, prospective, longitudinal studies investigating the relationship

between stress and ART treatment outcomes indicate that the higher levels of

negative psychological symptoms reported by female IVF patients may be

associated with lower conception rates. Salvatore et al. (2001) conducted a

study comparing the psychopathology, personality features, and marital

relationships of women undergoing IVF with those of a control group of patients

as well as comparing infertility patients participating in their first IVF treatment

cycle with those who were participating in their second or more IVF treatment

cycle. Results of this study indicated that while there were no significant

associations between any special psychopathological, personality, or marital

characteristics and pregnancy rates, women who achieved pregnancy through

IVF showed a statistically significant difference in their less exclusive closeness

with partners and their search for friendships and social contacts. Demyttenaere

et al. (1998) found in a series of studies that pre-cycle levels of negative

emotions were significantly associated with lower pregnancy rates. Further

analysis revealed that women with a lower score (i.e., fewer negative emotions)

than the median had a 31.3% chance of conceiving as compared to a 14.9%

chance of conceiving for women who had a higher score than the median. A

similar study conducted by Boivin and Takefman (1995) also supports the theory that stress is related to IVF outcome. Their results demonstrated that women who did not conceive as a result of the IVF cycle reported higher levels of stress during specific stages of the treatment cycle and had a poorer biologic response to treatment than those women who did conceive. Thiering et al. (1993) found that women starting their second or more attempt (referred to as veterans) scored significantly higher than those women initiating their first attempt with IVF (referred to as inductees). In addition, the veteran women had a significant association between depression levels and conception rates during the one-year follow-up period; 13% of depressed women conceived as compared to 29% of nondepressed women. The results of two studies conducted by Sanders and Bruce (1997, 1999) provided similar results demonstrating a significant difference among women participating in an IVF-ET treatment cycle in the levels of state anxiety between those who conceived and those who did not conceive. Creach-Le Mer et al. (1999) reported that an increase in increments of 10 points on an anxiety scale was associated with a twofold increase in the probability of failure for conception, leading the authors to assert that the treatment of anxiety in IVF patients should increase conception rates. Additional studies support these findings including studies conducted by Kee et al. (2000), Smeenk et al. (2001), and Klonoff-Cohen et al. (2001). Kee et al. (2000) found that among women entering an IVF program in Korea, those who failed to conceive had significantly higher pretreatment levels of anxiety and depression than those women who did conceive. Similarly, Smeenk et al. (2001) and Verhaak et al. (2001) found a

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significant relationship between baseline psychological factors and the probability of conception. Additionally, Klonoff-Cohen et al. (2001) found a significant relationship between baseline measures of psychological state and subsequent pregnancy rates. Gallinelli et al. (2001), in an investigation of the influence of anxiety as well as coping skills on conception rates, found that anxiety state score was significantly lower in patients achieving implantation than in the group who failed to conceive. In addition, women who had successful implantation had significantly lower systolic blood pressure and heart rates during the stress test than those women who failed to achieve implantation.

Researchers approaching the investigation of the relationship between stress and ART outcomes through measurements of psychoendocrinologic responses have also found similar results. In a series of studies, Demyttenaere et al. (1991, 1998) found that women with high anticipatory state anxiety levels and high anticipatory cortisol levels have lower pregnancy rates. Similarly, Strauss et al. (1992) found a reduced probability for patients with psychological impairment to achieve pregnancy. Facchinietti et al. (1997) found similar results. This study investigated a variety of variables as predictors for achieving pregnancy. The data provided evidenced a negative correlation between stress and outcome following an IVF-ET cycle.

However, a number of investigators exploring the relationship between stress and ART outcomes have reported findings that contradict the aforementioned studies. Lovely et al. (2003) recently conducted a study that measured cortisol and 6-sulfatoxy-melatonin in women during an IVF treatment

cycle. In addition to these measures of the physiologic stress response, participants completed the State-Trait Anxiety Inventory (STAI). The authors of this study did not find any statistically significant difference in any of the three variables in a comparison with a control group of donor IVF patients, leading to the conclusion that stress does not play a role in IVF outcome. In another study conducted by Harlow et al. (1996), while women who did not achieve pregnancy as a result of their IVF cycle reported higher levels of anxiety during the follicular and pre-operative phases, these findings were not statistically significant. Merari et al. (1992) found similar results in their investigation of 113 Israeli couples initiating their first IVF cycle. In this study, psychological assessments were conducted at three points in the treatment cycle: prior to beginning the cycle, the morning of oocyte retrieval, and the morning of embryo transfer. Results of this investigation found no significant differences between women who conceived and those women who did not conceive at any point in psychological assessments. In addition to these studies, Slade et al. (1997) also found no significant relationships between emotional state and conception rates. Furthermore, a recent study conducted by Csemiczky et al. (2000) also found no significant relationships between state anxiety levels and IVF conception rates for women presenting with tubal infertility.

Few studies address the provision of psychoeducational interventions for couples in the midst of their infertility procedures (Domar & Seibel, 1997; McNaughton-Cassill, 2000). In addition, a lack of systematic appraisal of the most effective form of psychological counseling or support is an impediment to

research. Traditional psychological treatment has included individual

psychotherapy and support groups. While clinical case studies point to the

benefits of these approaches, well-controlled studies that support the efficacy of

a traditional psychotherapeutic approach are very limited. In addition, while there

have been anecdotal reports of an increase in conception rates, little convincing

empirical evidence exists in the literature (Domar et al., 1990). Most studies

focusing on infertility counseling are limited in both the size and scope of the

examination and is based upon the assertions of counselors rather than any

systematic evaluation of the problems experienced by couples and methods

employed to resolve them. However, when investigations have been conducted,

the benefits of psychoeducational interventions to infertility couples have been

reported. In one report by Karahasanglu et al. (1972) examining the efficacy of

the use of counseling, four major areas were addressed: 1) screening and initial

evaluation of the couple, 2) relationship improvement, 3) sexuality, and 4)

supportive counseling. In this investigation, marked improvement in the

spontaneity and frequency of marital sexual intercourse occurred; attitudes

became more positive; tension between the couple diminished; husbands

became more actively interested; and the sense of isolation was decreased in

both the husband and wife (Seibel & Taymor, 1982; Karahasanglu et al., 1972).

Additional evidence concerning the therapeutic effectiveness of counseling

comes from investigations by Bresnick & Taymor (1979) who investigated the

effects in 62 infertile couples of five to six sessions of counseling on emotional

symptoms, relationship issues and the attitudes to infertility. Results of this

investigation demonstrated some improvement in symptomatology, leading the authors to conclude that infertility counseling improves the quality of life for many dealing with the crisis of infertility. However, Cooper (1979), investigating the effectiveness of a counseling support group offered through Resolve, Inc. as compared to a control group receiving no treatment, reported different results. Measures of locus of control, self-concept and body-image were taken before and after a 15 week therapeutic intervention. No differences between the two groups were observed. However, Cooper asserts that 15 weeks may not have been adequate time for adaptation to occur (Bresnick & Taymor, 1979; Cooper, 1979; Edelmann & Connolly, 1986). Examinations of the benefits of group sessions have also demonstrated a decrease in the amount of distress and feelings of personal failure experienced by infertile couples when they were able to vent their feelings and anxieties with others who were dealing with infertility. Another report focusing on therapeutic techniques that included patient education, encouragement, and behavioral techniques documented similar benefits (Abarbanel & Bach, 1959; McGuire, 1975; Berger, 1977; Seibel & Taymor, 1982).

Benefits of similar programs are documented in a report by McNaughton-Cassill et al. (2000). A brief couples' therapy group program was implemented at Wilford Hall Medical Center in Texas as an option for couples undergoing IVF treatment. In this study, participants were recruited by the nurse coordinating their IVF cycle. The groups met twice a week for 1.5 hours for the duration of their treatment cycle with one or two facilitators: a psychiatrist and a

psychologist. The groups used a Cognitive Behavioral format in which cognitions

or thoughts are believed to play a major role in one's evaluation of stressful

events and perceived coping resources. Within this context, participants were

encouraged to identify their own cognitions about their infertility and to explore

the associations between their irrational beliefs and expectations and emotional

distress. In addition, participants were introduced to techniques for reframing

attributions and generating alternative thoughts and solutions for common

problems. A number of common infertility-related themes including concerns

about isolation, problematic interactions with family and friends, compromised

marital relations, jealousy and inadequacy when confronted with normal fertility,

religious faith, and the ethics and morality of IVF procedures emerged through

the progression of the program. Participants frequently remarked that talking to

others going through similar experiences was reassuring. In addition,

participants frequently wanted to compare notes about the procedures they were

undergoing, including side effects of medication and the stress they experienced

as a result of either giving or receiving injections. Couples engaged in animated

conversations about medical procedures, the outcomes of previous attempts,

and how previous experiences related to their current experience. Couples

shared information with each other regarding national support networks as well

as the specifics about adoption options. Another benefit resulting from this

support group included the bonds formed among the participants extended

beyond the confines of the formal meetings into social interactions outside of the

program. In addition to these benefits realized as a result of the program, overall

results of this study found that both males and females valued the social support derived from the group and that the groups helped them to deal with the stress of IVF treatment. Couples also indicated that the program would be beneficial to others undergoing similar procedures and that participating in the support group was crucial to the management of their stress associated with the IVF treatment (McNaughton-Cassill et al., 2000).

In addition to these investigations, increasing evidence exists demonstrating that psychoeducational programs may be efficacious in the treatment of the emotional effects of infertility and may lead to increased conception rates. Results demonstrate that in women with idiopathic infertility, the elicitation of the relaxation response reduces anxiety, depression, anger, and fatigue while increasing a sense of well-being (Domar et al., 1990). Furthermore, the results of one study conducted by Domar et al. (1990) support the hypotheses that the reduction in stress increases the potential for conception. In addition to the documented and subjective improvement in psychological and physiological symptoms, 34% of the participants conceived within 6 months of completing the program (Domar, 1990). Similar findings were reported in a subsequent study conducted by Domar et al. (1992) with participants demonstrating statistically significant reductions in every factor measured including anxiety, depression, and anger. Again, 34% of the participants conceived within 6 months of completion of this program. Among those who conceived, 37% attempting in vitro fertilization conceived on their first attempt (Domar et al., 1992; Domar & Seibel, 1997).

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Methodological Issues

Several problems have been identified in the studies attempting to show a causal relationship between psychosocial stress and infertility. One criticism is that various types of fertility disorders are lumped together. Treating all fertility disorders in one study may dilute the magnitude of the effects of stress because infertility is a complex entity. Moreover, not all stressors that induce a stress response are relevant to reproductive failure. A second criticism revolves around the inability to separate cause from effect. Infertility and emotional distress can be viewed as a circular series of life crises and a variety of emotions ranging from hope to despair. Based on available evidence, the relationship between infertility and emotional distress is best described as reciprocal: infertility leads to emotional distress; emotional distress, in turn, may make conception less likely which leads to still more stress. Although a positive correlation between infertility and emotional distress has been found one cannot identify whether infertility is the cause of the emotional distress or whether the emotional distress is an etiological factor in infertility.

Similar to the criticisms about stress research in its totality, the term stress in the field of infertility has been a source of much conceptual confusion and has been defined in several different ways. The first common conceptualization of stress in infertility research is as an event defined as a distressing circumstance external to the person. Stress in infertility research has also been conceptualized as a response defined as a disturbance of a person's normal state. Finally, a third psychological conceptualization of stress in infertility research postulates

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that stress is determined neither by events nor by response variables. Alternatively, stress is viewed as a combination of many factors including the perceived meaning of an event and a self-appraisal of the adequacy of coping resources. Similarly, chronic stress has been defined as a set of related events and conditions that are perceived to threaten important social roles or "domains" that persist over a given length of time.

In addition to the lack of a clear, consistent conceptual framework of the stress process and its relationship to infertility, methodological problems in the design and analysis of studies have hindered infertility stress research efforts. One limitation cited is the use of convenience samples and/or small sample sizes. Other methodological issues may have contributed to conflicting results include homogenous groups of women in terms of ethnicity, age, and socio-economic status included in the samples. The limited representativeness of infertility patients seeking medical treatment has severely threatened the generalizability of these investigations. Because most of the psychologically oriented literature on infertility has focused on couples seeking medical treatment, most of which participate in IVF treatment protocols, the samples included in the studies represent only a select group of infertility patients and do not necessarily represent the treatment population as a whole. Furthermore, it can be argued, that these participants may in fact represent the most physically, psychologically, socially, and financially fittest group of infertility patients, with perhaps the most stable marriages (Schneider, 2000).

In addition, much of the research on this topic is based on nonexperimental and retrospective designs. Several statistical models using combinations of biomedical factors in relation with in vitro fertilization outcomes demonstrate limited external validity because they are based only on stable variables. Additionally, in the area of infertility, even well-designed, randomized, controlled trials rarely have sufficient statistical power to demonstrate small but clinically significant differences between control and treatment groups (Hughes, 1992; Smeenk et al., 2001; Wilson & Kopitzke, 2002). Furthermore, empirical evidence collected through a multitude of studies demonstrates that stress levels are not within the clinical range (Berg & Wilson, 1990; Benazon, 1992; Schneider, 2000). Supporting the crisis model proposed by Menning, psychological distress may be elevated at particular points in time and vary throughout the treatment process. However, overall distress levels have not been found to be extreme or debilitating. Therefore, psychological strain as opposed to psychiatric morbidity has generally characterized the distress experience by infertility patients (Daniluk, 1988; Seibel & Taymor, 1982; Berg & Wilson, 1990; Schneider, 2000). Based on this accumulated evidence, the use of psychological measures designed to detect psychopathology not specific to infertility may be inappropriate for infertility related investigations. The use of inappropriate measurement instruments may reduce the likelihood of detecting important differences. While attempts have been made to develop instruments measuring stress specific to the infertility experience, these measures may also be limited in capturing the multiple dimensions of infertility distress. In addition,

traditional psychological measures of depression, anxiety, and marital adjustment

appear to be the measures of choice by infertility researchers.

Meta-Analysis in Research

Definition, Development and Use of Meta-Analysis in Secondary Research

Research literature is growing at an exponential rate. As research results

continue to accumulate, interpreting results and finding the knowledge contained

in this flood of information becomes increasingly difficult. In the traditional

method of integrating research studies, a reviewer provided a narrative and a

chronological discourse on previous findings. However, this method is flawed

and inexact:

- This method is unable to deal with a large number of studies on a given

  topic. Therefore, reviewers focus on a small subset of studies, often

  without describing how those studies in the subset were selected.

- The conclusions of previous reviews conducted are often cited without a

  critical examination of the original reviewers.

- Reviewers are generally active and prominent in the field under review.

  Therefore, evidence contradictory to their own positions may be ignored,

  introducing bias as a factor in a reviewer's conclusions.

Addressing these issues, Gene Glass proposed a method to integrate and

summarize the findings from a body of related research in 1976. He first used

the term "meta-analysis" which he asserts is a philosophy, not a statistical

technique. Glass argued that a review of the literature should be as systematic

as primary research and should interpret the results of individual studies in the

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overall context of the findings. In a meta-analysis, relevant research studies are collected, coded, and interpreted using statistical methods similar to those used in primary data analysis. The result is an integrated review of findings that is more objective and exact than traditional reviews. According to Hunt (1997), several benefits of conducting a meta-analysis have been identified:

- Physicians can now make decisions regarding the use of therapies or diagnostic procedures on the basis of a single article that synthesizes the findings of a multitude of clinical studies.

- Researchers in every field can gain a coherent view of the central reality behind the multifarious and often discrepant findings of research in their field of interest.

- Meta-analysis of a series of small clinical investigations of a new therapy often provides a finding that physicians can confidently begin using without waiting long years for a large-scale trial to be conducted.

- Meta-analysis can generally synthesize differing results. When it cannot, it can often identify the moderator and mediator variables that account for the differences leading to the identification of precise areas in which future research is needed.

- In the context of social problems and the development of social policy, meta-analysis offers policymakers easily assimilated syntheses of relevant research that policymakers generally do not have the time or the training to evaluate independently.

Over the past three decades, meta-analysis has grown from an unheard preoccupation of a very small group of statisticians working on problems of research integration in education and psychotherapy to a minor academic industry encompassing an assortment of procedures used in a variety of disciplines. Its popularity in the social sciences and education pales in comparison to its influence in medical research (Rosenthal, 1978; Hedges, 1985; Hunt, 1997; Hoffert, 1997).

Meta-Analysis in Medical Research

Evidence-based medicine has been given increasingly more emphasis over recent years. Evidence-based medicine focuses on the examination of empirical evidence from clinical research for sound medical decision-making. It is especially useful in providing information regarding the strength and quality of empirical evidence either supporting or refuting a medical practice as well as for developing practice guidelines. In medical research, meta-analysis uses the accumulated evidence about a treatment or procedure to provide guidance to clinicians and to suggest directions for future study. The use of meta-analysis in the medical literature has generated considerable interest and has proven to be a powerful tool in the field of perinatology. Likewise, obstetrics is one field leading other medical specialties in the attempt to systematically review all randomized trials conducted in its discipline (Hughes, 1992; Peipert & Bracken, 1997).

There are several advantages to conducting a meta-analysis, particularly in medical research. First, the researcher is able to identify gaps, problems and limitations in the primary research base. Since research regarding the

relationship between stress and ART treatment outcomes have led to conflicting results, this technique can help researchers to resolve some uncertainty and controversy in this field. Through increasing sample size, meta-analysis can provide stronger evidence for or against a treatment effect than can be derived from any of the individual studies because a more precise estimate of the effect size or measure of association is generated. This also increases statistical power allowing small but clinically significant differences to be detected. In addition, meta-analysis allows researchers to investigate research questions not posed at the start of an individual treatment trial. Finally, another major advantage of this type of research review is the opportunity for others to judge the quality of its conclusions (Hughes, 1992; Peipert & Bracken, 1997).

Summary

Although sometimes seen as a social condition of childlessness, infertility is a significant health problem. The role of stress on infertility and treatment outcomes is complex, often leading researchers to conflicting conclusions. The psychological impacts of infertility have been well documented in the literature. While research findings regarding the prevalence of distress and depressive symptoms in infertile women are inconsistent, there is evidence to support that at least some women who confront infertility are at risk for heightened distress and depressive symptoms. Furthermore, infertility treatment protocols including ART programs are considered the most invasive and expensive treatments available to couples. Because ART treatment programs can exact a high toll on couples physically as well as financially and are generally the last treatment option

offering hope to couples trying to conceive a child, these patients may experience the greatest amount of distress. Psychoeducational interventions may provide an important component to the treatment of infertility. In addition, these programs may prove to be an effective intervention in preventing the anticipated increase in psychological distress as the duration of infertility increases. While several theoretical models postulate the effects of stress on infertility and infertility treatment outcomes as well as the efficacy of psychoeducational interventions, a synthesis of the accumulated data incorporating a qualitative assessment of the methodology of reviewed studies as well as a quantitative method of combining and analyzing the data examining the effects of stress on ART treatment outcomes is nonexistent. Therefore, this study will investigate through a meta-analytic review of primary research studies conducted to date the impact of stress on the success of ART treatments and to determine whether psychoeducational interventions mitigate the impact of stress during ART treatments.

CHAPTER THREE: METHOD

Problem Statement

The psychological impacts of infertility have been well documented in the literature. While research findings regarding the prevalence of distress and depressive symptoms in infertile women are inconsistent, there is evidence to support that at least some women who confront infertility are at risk for heightened distress and depressive symptoms. Psychoeducational interventions may provide an important component to the treatment of infertility. In addition, these programs may prove to be an effective intervention in preventing the anticipated increase in psychological distress as the duration of infertility increases. While several theoretical models postulate the effects of stress on infertility and infertility treatment outcomes as well as the efficacy of psychoeducational interventions, a synthesis of the accumulated data incorporating a qualitative assessment of the methodology of reviewed studies as well as a quantitative method of combining and analyzing the data examining the effects of stress on ART treatment outcomes is nonexistent.

Research Purpose, Questions and Hypotheses

Although sometimes viewed as a social condition of childlessness, infertility is a significant health problem. The role of stress on infertility and treatment outcomes is complex, often leading researchers to conflicting

conclusions. The purpose of this study was to investigate the impact of stress on the success of ART treatments and to determine whether psychoeducational interventions mitigate the impact of stress during ART treatments through a synthesis of the research. According to Cooper (1982), the goal of an integrated review of the research is to summarize the accumulated knowledge concerning the relations of interest. An additional goal of an integrated review is to highlight important issues that research has left unresolved. The goal of this review was to answer two research questions:

1. What is the relationship between stress and Assisted Reproductive Technology (ART) treatment outcomes?

2. Do psychoeducational interventions mitigate the distress experienced by patients participating in an Assisted Reproductive Technology (ART) treatment regimen?

Therefore, the two hypotheses that were tested in this meta-analysis include:

1. Increased levels of stress will reduce the likelihood of Assisted Reproductive Technology (ART) treatment success, and

2. Psychoeducational interventions provided to patients receiving infertility treatment will mitigate the effects of stress during Assisted Reproductive Technology (ART) treatment.

Method

Formulation of the Research Problem

The primary goal of research synthesis is the integration of empirical

evidence for the purpose of producing generalizations. There are three purposes

inherent in an integrated research review:

1. A critical analysis of the research, paying particular attention to

    relevant theories,

2. An attempt to resolve conflicts in the literature, and

3. An attempt to identify current issues to be addressed in future

    research.

There are four primary processes that transpire in a research synthesis:

1. The formulation of the problem,

2. The collection of data and research studies,

3. The evaluation of the data, and

4. The analysis and interpretation of results.

Because research synthesis is an integration of studies, primary research

on a topic must exist. The formulation of the problem can arguably be the most

important aspect of a research synthesis, requiring considerable thought and

planning. The consideration and decisions made during the formation of a

problem will directly influence data collection, the evaluation of the data, as well

as the presentation of the findings. One key issue to be addressed when

developing a problem to research through a meta-analysis is the

conceptualization and definition of the problem. This includes considerations of a

number of characteristics inherent in the problem. For example, is the problem conceptually a broad topic or is it a narrowly defined topic? In addition to the definition of the problem, the researcher must also specify the universe to which the researcher wishes to generalize. There are two models of generalizations in which a researcher can approach a meta-analysis. The most common approach in quantitative research synthesis is the fixed effects (conditional) model. In the fixed effects model, the generalizations and inferences are made only of the studies that have actually been conducted and are observed in the meta-analysis sample. The second model is the random effects (unconditional) model which presumes that the sample of studies included in the meta-analysis represents a sample from a hypothetical collection of studies. Therefore, generalizations and inferences can be applied to other studies or other situations that could have been studied (Hedges, 1994).

In this study, both hypotheses were analyzed through a random effects model. The random effects model is conceptually justified for this study in that it was expected that the studies included in the analysis will differ from one another in study characteristics and in effect size parameter. In addition, based on prior criticism regarding homogenous groups represented in the samples of infertility research, a random effects model asserts that the studies to be included in the analysis differ from the possible studies in the universe as a consequence of sampling procedures. The conceptualization of this study implies that the studies included in the analysis are different from one another in ways too complex to capture by the inclusion of simple study characteristics. Therefore, inferences

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can be generalized to other studies or other situations that could have been

studied. It provided this researcher with the ability to provide information

regarding the likely relationship between stress and ART treatment outcomes.

Another fundamental issue in the formation of a problem to be addressed

with a meta-analysis is the nature of the effect size parameter to be estimated.

Theoretical effect sizes, which remove biases due to artifacts of study design,

can systematically influence effect size. Operational effect size parameters

represent the true or population relationship measured between variables

measured in a study without correcting for biases. Therefore, operational effect

size parameters can be systematically influenced by artificial sources of bias

such as restriction of range and measurement error present in a particular study.

Although most research syntheses employ operational effect size parameters,

some researchers use theoretical effect sizes to enhance the comparability and

combinability of estimates across studies whose operational effect size would be

influenced substantially because of biases or study design and features.

Although some authors have argued that a meta-analyst should not correct for

study imperfections or artifacts and estimate only the operational effect size

parameters, Hunter and Schmidt (1994) contend that these artifacts are artificial

in nature, stemming from imperfection in research methods. Therefore, they

recommend estimating theoretical effect size parameters arguing that correcting

these imperfections is essential to the development of cumulative knowledge

(Hedges, 1994). As noted by Hunter and Schmidt (1990), the largest source of

the variability across study effect sizes is sampling error. The removal of the

variability across studies that can be attributed to sampling error will therefore provide a more accurate estimate of the true variance across study effect sizes. For the purposes of this meta-analysis, correction to the statistical artifact of sampling error was made, estimating the theoretical effect sizes.

Although it is important to control and estimate bias in primary research studies, the reduction of bias and similar errors is of great importance when conducting a meta-analysis over a culmination of studies. Although corrections of problems in the design of the primary studies cannot be made, methods for measuring errors in study findings due to study imperfection and ultimately correcting these errors in a meta-analysis should be conducted. Errors in primary research studies can be either systematic or unsystematic. Examples of unsystematic errors include sampling error and bad data such as errors in statistical analysis and improper administration of the measurement instrument. An example of a systematic error includes attenuation of the population correlation. To address systematic errors in this meta-analysis, primary research studies were weighted by sample size and an index of study quality when combining the observed effect sizes across studies as described later in this chapter (Wortman, 1994.)

Identification of Studies

Once the researcher has formulated and clearly defined the question to be addressed with the meta-analysis, a literature review for the collection of relevant data and studies is conducted. The purpose of data collection is to locate studies that are representative of the intended universe of studies related to the topic of

interest. Therefore, it is essential that the search criteria are consistent with the definition of the problem. If the search criteria used are consistent with the definition, the studies yielded are considered to be an exhaustive sample which is a representative sample of studies of the universe. The point of conducting an exhaustive review of the literature is to avoid missing a useful study. One way in which to improve the yield in a research review is to search multiple bibliographic databases. A second approach to improving the identification of relevant studies is through citation searches which provide papers comparable in utility and centrality to those produced through the database search. In addition to citation searches, footnote chasing can provide additional primary studies of interest. Finally, consultation through informal conversations with others in the field can also be helpful in locating usable studies. The ideal literature review will provide the best possible pool of primary studies from which to select those studies finally included in the analysis (White, 1994).

Researchers conducting a literature review for a meta-analysis must recognize potential threats to the validity of the studies included in the final analysis. One such threat is publication bias. In many cases, the decision to publish will be influenced by whether or not the findings yielded statistically significant results, with significant results more likely to be published. Therefore, a preponderance of the publications retrieved through an exhaustive literature review is statistically significant. If the meta-analysis includes only those published studies, there is a risk that it will lead to biased conclusions. Researchers can employ two techniques to avoid the problem of publication bias.

First, this problem can be circumvented by restricting the meta-analysis to

include only those studies selected on the basis of a sampling frame such as

through the use of a registry of prospective trials. The use of registered trials

requires the inclusion of data from the registered studies that are unpublished

and are unaffected by the results of the study. However, the most common

method for avoiding publication bias is by attempting to track down all relevant

unpublished studies on the topic. This can be accomplished through a variety of

techniques such as following up on published abstracts and contacting

knowledgeable researchers in the field for leads on studies known to have been

conducted. This would include searching for relevant studies among

dissertations and master's theses as well as investigating presentations of

unpublished studies at meetings and conferences. Although either of these

methods will assist the researcher in avoiding publication bias, even with the

greatest of care given to identifying unpublished research, the researcher can

never be sure that all or even most of the unpublished work has been located.

Analytical tests have also been developed to correct for publication bias. One

such method is the file drawer test which determines how many studies with

nonsignificant findings would be necessary to negate the meta-analysis findings.

Most recently, more sophisticated methods using a weighted distribution theory

to correct for publication bias have been developed. Although these analytic

techniques are available to identify and correct publication bias, the statistical

properties of these methods have yet to be subjected to scrutiny. Therefore,

these methods are generally not considered to be standard methods employed in

a meta-analysis (White, 1994; Rosenthal, 1994; Dickersin, 1994). In this study, several methods were utilized in an effort to avoid and diminish publication bias.

Studies included in this meta-analytic review were first located through an exhaustive comprehensive search of the English language literature from January 1985 through December 2003. Electronic searches were performed on MEDLINE/PubMed (1985 – 2003), ERIC (1985 – 2003), Psychinfo (1985-2003), and Dissertation Abstracts Online (1985 – 2003) databases. (A description of each database may be found in Appendix A). Although the search strategy varied depending on the database, search terms for the first hypothesis included: "infertility" and "psychological stress" or "anxiety"; and any terms related to "assisted reproductive technology" such as "In Vitro Fertilization", "Gamete Intrafallopian Transfer", or "Zygote Intrafallopian Transfer" and "stress" or "anxiety". Search terms for the second hypothesis included: "infertility" and any terms related to coping such as "psychological adaptation" or "group psychotherapy"; and "conception" or any terms related to "assisted reproductive technology" such as "In Vitro Fertilization", "Gamete Intrafallopian Transfer", or "Zygote Intrafallopian Transfer" and "stress management" or "support groups" or any terms related to "coping", such as "psychological adaptation" or "group psychotherapy". Following the search of relevant databases, manual scans of reference lists and other publications, as well as branching from primary studies and review articles was conducted to identify any additional studies left uncovered in the original search.

To address potential publication bias, a search for registered clinical trials being conducted in the field of reproductive endocrinology was conducted. Specifically, a search identifying any clinical trial involving either the relationship between stress or distress and ART treatment outcomes or the impact of psychoeducational interventions on stress and distress experienced by patients participating in an ART treatment program was conducted. The second method addressing publication bias included contacting professionals active in conducting research in this field. Correspondence with these professionals was initiated in an effort to identify any other unpublished research studies in this field. In addition, efforts to track original study results on published abstracts from professional conferences including the American Society of Reproductive Medicine annual conference was made.

In order to reduce selection bias and increase internal validity, this researcher reviewed each article identified in the literature review. The purpose of this review was to ensure all articles and studies meeting specified criteria for inclusion in the meta-analysis were identified. For each hypothesis, each study met all of the following inclusion criteria:

1. For hypothesis one, the study must involve situations where women were participating in an ART treatment program and the focus of the study was on the relationship between stress and ART treatment outcomes. For hypothesis two, the study must involve women participating in a psychoeducational intervention program and an ART

treatment program. In addition, the study must focus on the

relationship between the psychoeducational intervention and stress.

2. The study must have been conducted between January 1985 and
December 2003 and be prospective in design.

3. The study must report outcome measures of stress or anxiety and
treatment outcomes. For hypothesis one, treatment outcome is
defined as achieving pregnancy or failure to achieve pregnancy. For
hypothesis two, treatment outcome is defined as the post-treatment
score. Studies with insufficient data for effect size calculations will be
excluded.

Using the above inclusion criteria, studies from electronic searches, references

from primary studies and review articles were examined to identify potential

studies for inclusion. Following this procedure, the collected studies were

reviewed by this researcher to identify all studies meeting these criteria for

inclusion in the meta-analysis.

In attempting to obtain all of the research, published and unpublished, on

the topic of interest, it is inevitable that similar reports based on the same

research study may be retrieved. For example, after completing research for the

completion of a dissertation or thesis, a researcher will often present the results

at a conference or publish the research in a professional journal. In the event

that reports appeared to be based on the same research, the author was

contacted to verify the uniqueness of these reports. If a choice was presented

between an unpublished version of the research such as in a dissertation or

thesis versus a published report of the research, the report containing the most information in terms of reporting outcomes was given priority and was used as the reference of choice in this review.

Evaluation of Data

Coding the Quality of the Studies

Once the studies were identified and adequate information was available, each study was subjected to a structured review of the quality of the study. This review applied the validity framework developed by Campbell and his associates, providing a matrix of designs and study features or "threats to validity" (Wortman, 1994). The design features of this framework incorporate four categories. First, internal validity refers to the truthfulness regarding statements that can be made about whether there is a causal relationship from one variable to another in the form in which the variables were manipulated or measured. External validity is defined as the "approximate" truthfulness in the generalizations made about the presumed causal relationship across different persons, settings, and times. Next, statistical conclusion validity refers to the truthfulness of the conclusions drawn about covariation between the identified independent and dependent variables. Finally, construct validity refers to the approximate truthfulness with which a researcher can make generalizations regarding the higher-order constructs from the research operations. In this study, construct and external validity was used to determine if a particular study satisfied the hypothesis with respect to the cause, effect(s), participants, and setting. In this synthesis, the

construct of cause for hypothesis one was identified as stress while the construct

of effect included ART treatment outcomes defined as whether or not pregnancy

was achieved. For hypothesis two, the construct of cause was identified as the

psychoeducational intervention while the construct of effect was defined as the

stress experienced. The participants examined for both hypotheses in this meta-

analysis were infertile women participating in ART treatment programs. If a given

study met these criteria, then it was considered to be relevant for the inclusion in

this synthesis. Internal validity was established through identifying only those

studies employing prospective designs. Statistical conclusion validity was

established by excluding those studies that applied inappropriate statistical tests

that cannot be corrected by the meta-analyst or inappropriate grouping or

comparisons in the analyses. The structured review of the studies for this meta-

analysis is presented in Appendix B. Each question was scored as 1 for yes

responses and 0 for no responses. The investigator then generated a summary

score for each group of items and used the average of these summary scores to

indicate the quality of each study.

Coding the Studies

Once all relevant studies have been retrieved, the meta-analysis

researcher must then determine the characteristics of interest within the studies.

Conventions for coding these characteristics must then be developed. Finally,

coding forms capturing the characteristics present in each study must then be

constructed. The purpose of coding study characteristics is to ensure the reliable

and orderly extraction of information from each of the studies. This provides

information regarding the quality of each study as well as the adequacy of the information in each study. In addition, the synthesist should seek independent verification and compute reliability estimates. Key items to include in a coding system are as follows:

- Report identification such as the author, country, year, source of publication and coder of the study,

- Setting describing the general conditions of the study such as the scope of sampling, the involvement of special populations, and demographic information,

- Subjects including specific characteristics of the sample(s) and subsample(s) participating in the study,

- Methodology which describes the research design, details related to sampling and attrition, and the presence or absence of threats to internal validity,

- Treatment identifiers including the theoretical orientation motivating a treatment to be investigated, specific components of a treatment, the nature of the control groups, the duration of the treatment, and the mode of the treatment delivery, and

- The quantitative information required to estimate an effect size as well as items that describe the nature of the outcome measures (Stock, 1994).

Additionally, coding outcomes and study features will identify those methodological and substantive characteristics that may be responsible for

significant variations in the findings. For this study, characteristics reviewed and coded are presented in Appendix C, while the coding sheet appears in Appendix D and the coding manual and reference guide appears in Appendix E.

A pilot test of the master code sheet was conducted. Two professional evaluators meeting the following qualifications were recruited to participate:

- Completed a Doctor of Philosophy degree in Measurement and Research, and

- Current professional in the field of research and evaluation.

Training and implementation of the coding process were as follows: First, the two independent evaluators were furnished with a copy of a coder training manual and reference guide. Each coder used the manual and reference guide to code a single article independently. Next, the researcher met with each evaluator independently to discuss problems encountered in using the guide and the coding sheet, and to make any adjustments or changes to the guide, the coding sheet, or both as required. The two evaluators were then assigned to a random sample of all of the articles to code for each hypothesis. For hypothesis one, each evaluator received the same six articles to code. For hypothesis two, each evaluator received the same two articles to code. The code sheets submitted by the two evaluators were then compared to the master code sheet developed by the researcher. Items scored differently by either the researcher or by the two independent evaluators were discussed by the team. Item scores in disagreement were coded by majority decision between the three evaluators.

The percentage of agreement between codes assigned by a given coder and those established by the master code sheet, was then calculated.

Analysis and Interpretation

Study coding and data was compiled using Microsoft Excel XP spreadsheet to collect and organize the information. An Excel form was created to prompt for all needed features of each study and automatically save the information in a database from which the analysis was conducted. SAS 8.2 was used to perform the statistical tests needed for this study.

Effect Size

Studies that were selected for inclusion in the meta-analysis were analyzed to generate an effect size, a measure of the magnitude of the score change between the pre and post treatment, or conceived versus failure to conceive groups. For hypothesis one of this study, the effect size represents the direction, positive or negative, and magnitude of the influence of stress on ART treatment outcomes. For hypothesis two of this study, the effect size represents the direction, positive or negative, and magnitude of the influence of psychoeducational interventions on an individual's level of stress during ART treatment. The computation of effect sizes for outcomes comparison was based on one of the following:

1. Direct computation,

2. Results of significance tests reported in the study, and

3. Results from significance levels.

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The effect size metric that was used for each analysis was Cohen's d. Cohen's effect size provides a common scale for comparison of study outcomes reflecting the difference between estimated population means divided by average estimated population standard deviation. Effect sizes were computed using the most appropriate option listed in Table 2, depending on the data available in each study. Because of the complexity of conceptualization of stress in infertility research, the results of measures of stress may represent several constructs, multiple measures of the same construct, or both. When the results represent several different constructs, the effect sizes on all constructs and measures were coded. For example, results reported for anxiety as a measure of stress may utilize the State-Trait Anxiety Inventory (STAI). The STAI measures two distinct constructs:

1. State Anxiety evaluates how respondents felt at a particular time in the recent past and how they anticipate they will feel either in a specific situation that is likely to be encountered in the future or in a variety of hypothetical situations. In addition, it assesses the level induced by stressful experimental procedures and by unavoidable real-life stressors such as imminent surgery, dental treatment, job interviews, or important school tests. It is a sensitive indicator of changes in transitory anxiety experienced by clients and patients in counseling, psychotherapy, and behavior modification programs.

2. Trait Anxiety is typically used for screening high school and college students and military recruits for anxiety problems, and for evaluating

the immediate and long-term outcome of psychotherapy, counseling, behavior modification, and drug-treatment programs. It has been proven useful for identifying persons with high levels of neurotic anxiety and for selecting subjects for psychological experiments who differ in motivation or drive level.

Therefore, effect sizes were computed for both state anxiety and trait anxiety. Several different constructs were expected to be represented in the primary research studies including: state anxiety, trait anxiety, depression measures, mood assessments, and physiological measures of the stress response. When results from multiple measures of stress representing the same construct were reported for the same sample group in a study, Cohen's effect sizes were calculated for each measure and then averaged and weighted to provide one statistic for each study. Finally, many studies may assess the impact of stress measured at different times throughout the ART treatment program. For example, the STAI may be administered at the beginning of the treatment program before any medications have been administered, at the time oocyte retrieval, at the time of embryo transfer, and at the time of the pregnancy test. This time-series information provided an interesting analysis of temporal patterns in ART outcomes. Effect sizes for studies providing measures at multiple points during the treatment program were computed separately and compared across studies using univariate procedures.

Table 2

Effects size computation

Data Supplied	Effect Size Formula	Variable
1. Group means, standard deviation	$d = \dfrac{\overline{X_1} - \overline{X_2}}{\sigma}$	$\overline{X_1}$ = mean score of group 1 $\overline{X_2}$ = mean score of group 2 σ = pooled standard deviation
2. F statistic, df, N	$d = \dfrac{\sqrt{F}(n_1 + n_2)}{\sqrt{df}\,\sqrt{n_1 n_2}}$	F = F statistic n_1 = sample size of group one n_2 = sample size of group two df = degrees of freedom
3. Chi-square, N	$d = \sqrt{\dfrac{4(\chi^2)}{N - \chi^2}}$	χ^2 = chi-square N = total number
4. Correlation	$d = \dfrac{2r}{\sqrt{1 - r^2}}$	r = correlation coefficient
5. Significance level	$d = \dfrac{2t}{\sqrt{df}}$	df = degrees of freedom

Incomplete Reporting of Results

Even the most carefully planned research synthesis will encounter problems emerging from studies that do not provide comparable information. The problem of missing data occurs in an integrated review when studies do not report the relevant statistics on the outcome data or adequate descriptions of the methods needed in order to apply quantitative techniques for combining the results across studies. Three kinds of data required for conducting an integrated review may be missing. The first type of missing data includes studies that are

unavailable for use in a synthesis. In an effort to avoid this type of missing data, an exhaustive search of the literature including published and unpublished reports on the topic of interest as described earlier was conducted. In addition, studies that are to be included in a research synthesis may also lack relevant information on the variables that are thought to moderate effect size. Finally, studies identified and collected in the literature review may be missing the relevant information necessary for calculating a measure of the study's effect size. This problem arises when studies report no statistics or an inadequate amount of information about the outcome scores. In this meta-analytic review, studies that reported an insufficient amount of data to compute an effect size, the researcher was contacted in order to obtain all relevant information. In the event that information to compute an effect size is unobtainable, if the researcher describes the findings in terms of "non-significant" without reporting the associated statistic, an effect size of 0 was assumed. The use of this convention provided a conservative impact on the quantitative review results. For those studies describing a statistical test as reaching a particular level of significance rather than stating the exact probability associated with the outcome of the inference test, the probability was assumed to be equal to the stated value. This convention provided a conservative estimate of the significance level in each case (Piggott, 1994).

Combining Estimates of Effect Size

Because this study assumes a random effects model a priori, the population effect size for the ith study (θ_i) is assumed random with its own

distribution. Therefore, the total variability of an observed study effect size estimate (v_i^R) reflects both conditional variation of that effect size around each population (θ_i) and random variation of the individual θ_I around the mean population effect size. Therefore, the overall mean and variance of each effect size were determined, weighted by the sample size and study quality using the following formulas:

$$\overline{T}. = \frac{\sum\limits_{i=1}^{k} q_i\, w_i^R\, T_i}{\sum\limits_{i=1}^{k} q_i\, w_i^R} ,$$

where

$\overline{T}.$ = an unbiased estimate of the population parameter θ,

w_i^R = weight assigned to the ith study computed as $w_i^R = \dfrac{1}{v_i^*}$,

q_i = the ith study's score on the quality index, and

T_i = one observed effect size in the ith study with a population effect size

of θ_i and variance v_i.

Using the weights described above, the conditional variance of the average effect size $\overline{T}.$ was computed as follows:

$$\mathrm{var}(\overline{T}|\Delta) = \frac{1}{\dfrac{\left(\sum q_i^2\, w_i^F\right)}{\left(\sum q_i\, w_i^F\right)^2}}$$

where

$$w_i^F = \frac{1}{v_i}$$

where

$$v_i = \frac{n_i^1 + n_i^2}{n_i^1 n_i^2} + \frac{d_i^2}{2\left(n_i^1 + n_i^2\right)},$$

where

n_i^1 = within-study sample size in group 1 of the ith study,

n_i^2 = within-study sample size in group 2 of the ith study, and

d_i = estimates the population parameter θ_i.

The specific effect size statistic used to estimate T_i is the standardized mean differences. The following formula was used to compute the standardized mean differences:

$$d_i = \frac{\overline{X}_i^1 - \overline{X}_i^2}{s_i},$$

where

$\overline{X}_i^1$ = the mean of group 1 in the ith study,

$\overline{X}_i^2$ = the mean of group 2 in the ith study, and

s_i = the pooled standard deviation of the two groups.

The following formula was used to compute the variance:

$$v_i^* = \sigma_\theta^2 + v_i,$$

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where

σ_θ^2 = between-studies variance or the variance component which serves

as an estimate of the weighted sample estimate of the

unconditional variance $\sigma^2(T_i)$ and computed as follows:

$$\hat{\sigma}_\theta{}^2 = [Q - (k-1)]/c,$$

where

$$C = \sum_{i=1}^{k} w_i^F - \sum_{i=1}^{k} w_i^{F^2} \Big/ \sum_{i=1}^{k} w_i^F, \text{ and}$$

v_i = within-study variance or the conditional variance and computed as

follows:

$$v_i = \frac{n_i^1 + n_i^2}{n_i^1 n_i^2} + \frac{d_i^2}{2(n_i^1 + n_i^2)},$$

where

n_i^1 = within-study sample size in group 1 of the ith study,

n_i^2 = within-study sample size in group 2 of the ith study, and

d_i = estimates the population parameter δ.

The following formula was used to correct for sampling error, providing for an

unbiased estimate of the variance:

$$V_{(e)} = \left[\frac{\overline{N}-1}{\overline{N}-3} \right]\left[\frac{4}{\overline{N}} \right]\left[1\left(\frac{\overline{d}^2}{8} \right) \right]$$

where

$\overline{N}$ = mean sample size and

$\overline{d}$ = estimates the population parameter δ.

The unbiased estimate of the variance was then computed as follows:

$$uv = v_i^* - v_{(e)}$$

To determine whether or not the variance component differs significantly from zero, the following homogeneity test statistic was computed:

$$Q = \sum_{i=1}^{k} w_i^F T_i^2 - \frac{\left(\sum_{i=1}^{k} w_i^F T_i\right)^2}{\sum_{i=1}^{k} w_i^F} \, .$$

Q was rejected if the upper-tail critical value of chi-square at k-1 degrees of freedom (where k = number of groups) is significantly greater than what we would expect by chance if all studies shared a common population effect size. If the Q test for homogeneity of effect size was rejected, an estimate of the magnitude of the variance component was investigated. The standard error of the estimate of the combined effect size is equal to the square root of $v_.$ Multiplying the standard error by an appropriate critical value C_α (1.96, α = 0.05), and adding and subtracting the resulting product to $\overline{T}_.$ provided a 95% confidence interval for θ as follows:

$$\theta_L = \overline{T}_. - C_\alpha (\, var(\overline{T}|\Delta)\,)^{\frac{1}{2}}, \; \theta_U = \overline{T}_. + C_\alpha (\, var(\overline{T}|\Delta)\,)^{\frac{1}{2}}$$

The estimate of the variance component, σ_θ^2, provides a nonzero estimate of the variance component only if the homogeneity statistic Q is larger than its expected

value under the null hypothesis that $\sigma_\theta^2 = 0$. In addition, if the Q statistic was

rejected, then study effect sizes were disaggregated into appropriate categories

based on characteristics of the studies. Graphical displays depicting the

frequency distribution of effect sizes as well as the confidence interval are

provided for each individual study as well as for combined results. In the event

that studies have been disaggregated into categories, the studies were then

examined for any moderating effects that may be present.

Identification of Outliers

Following the computation of the overall mean and variance across

studies, the data was analyzed to identify potential effect sizes for outliers. The

identification of outliers is important in that these data could result in a notable

increase in the observed variance and a distortion in the mean, altering the

conclusions reached in this meta-analysis. Although the methodology for

detecting outliers in meta-analytic reviews is sparse, Huffcutt and Arthur (Arthur

et al, 2001) have proposed the Sample-Adjusted Meta-Analytic Deviancy

(SAMD) statistic. The SAMD statistic compares the value of each study effect

size computed without that effect size in the analysis and adjusts the difference

for the sample size of the study, resulting in one SAMD statistic for every primary

study included in the analysis as well as a distribution of SAMD statistics that

approximate a t distribution. Because SAMD values approximate the t

distribution, values greater than 3.0 were considered extreme and identified as

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potential outliers (Arthur et al., 2001). The equation for computing the variance is as follows:

$$v_{\bar{d}} = \frac{4 * (\bar{N} - 1) * \left[1 + \left(\bar{d}^2_{w/out\,study}\right) * 8\right]}{\bar{N} * (\bar{N} - 3) * k}$$

where

$\bar{d}$ = mean effect size,

$\bar{N}$ = average sample size of the studies, and

k = the number of studies used to compute the mean effect size.

The SAMD statistic is then computed using the following equation:

$$SAMD_i = \frac{d_i - \bar{d}_{w/o\,study}}{\sqrt{v_i + v_{\bar{d}}}}$$

where

$\bar{d}$ = mean effect size and

$\sqrt{v_i + v_{\bar{d}}}$ = standard error.

Statistical Analysis

A formal analysis was completed for the effect sizes utilizing a mixed effects linear regression model and weighted least squares estimation. The prediction model is as follows:

$$T_i = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2} + ... + \beta_p X_{ip} + u_i + e_i$$

where

β_0 = the model intercept,

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$X_{i1}, \ldots, X_{ip}$ = the coded characteristics of studies hypothesized to predict

the study effect size θ_i,

$\beta_1, \ldots, \beta_p$ = regression coefficients capturing the association between

study characteristics and effect sizes, and

$u_i + e_i$ = the random effect of study i (error term). (The deviation of study

i's true effect size from the value predicted on the basis of the

model. Each random effect is assumed independent with a mean

of zero and a variance $\sigma^2_\theta + v_i$.)

The regression was computed with the effect estimates as the dependent

variable and the predictor variables as independent variables with weights

defined by the reciprocal of the sampling variance. Therefore, a weighted least

squares approach was used to determine the optimal weights as follows:

$$w_i^R = \frac{1}{(\sigma^2_\theta + v_i)}.$$

In order to estimate σ^2_θ, and, therefore, the weights, w_i^R, the method of moments

procedure was used. In this procedure, provisional estimates of β's was

computed in three steps as follows:

1. Computation of estimates $\hat{\beta}_o, \ldots, \hat{\beta}_p$ using ordinary least squares

regression to yield a by-product of the residual sum of squares:

$$RSS = \sum \left(T_i - \hat{\beta}_o - \hat{\beta}_1 - \ldots - \hat{\beta}_p X_{ip} \right)^2,$$

2. Estimate σ^2_θ as follows:

$$E(\text{RSS}) = \text{constant}(1) + \text{constant}(2) * \sigma^2{}_o.$$

This equation is solved for $\sigma^2{}_\theta$ by substituting the observed sum of square residuals, RSS for the expected E(RSS), which led to the following estimate:

$$\sigma^2{}_\theta = \frac{[\text{RSS} - \text{constant}(1)]}{\text{constant}(2)}.$$ (When a negative number is produced, $\sigma^2{}_\theta$ will be set to zero.)

3. The new estimates of the regression coefficients were computed using weighted least squares regression with the weights provided as follows:

$$w^2{}_i = \frac{1}{(v_i + \sigma^2{}_\theta)}.$$

Two hypothesis tests were conducted. First, the null hypothesis for the regression coefficient β_q for any q = 0, …., p is as follows:

$$H_0 : \beta_q = 0.$$

In order to test this hypothesis, the ratio of the estimate to its standard error, depicted as follows:

$$t = \frac{\hat{\beta}_q}{S(\hat{\beta}_q)},$$

where S($\hat{\beta}_q$) is the estimated standard error of $\hat{\beta}_q$ which are produced by the weighted least squares regression procedure. The obtained *t* was then compared with the critical values of *t* with $k - p - 1$ degrees of freedom.

Finally, the null hypothesis for the random effects variance was tested and is as follows:

$$H_0 : \sigma^2_\theta = 0.$$

This hypothesis was tested by computing a weighted least squares regression with weights equal to $w_i^F = 1/v_i$. The weighted residual sum of squares was compared with the critical values of chi-square distribution with $k - p - 1$ degrees of freedom.

Interpreting the Results

When interpreting the overall result of the meta-analyses, a confidence interval was constructed to determine whether the average effect size under investigation encompasses zero. In addition, the use of Cohen's guidelines was used to evaluate significance of effect size defined as:

0.2 = small association,

0.5 = medium association, and

0.8 = large association observed.

Effect sizes are also reported for each variable. For hypothesis one, effect size comparisons were made with respect to the following variables: time of measure (baseline/pre-treatment, follicular phase, oocyte retrieval, embryo transfer, and luteal phase), construct (acute stress, chronic stress, and depression), duration of infertility and country in which the study was conducted. For hypothesis two, effect size comparisons were made for construct measured (acute stress, chronic stress, and depression).

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Generalizability

One strength of this study is that it allows the relationship between stress and achieving pregnancy through ART treatment protocols to be estimated across populations, at different times of the ART program, and study designs. It was hoped that the results of the first analysis would provide adequate information to resolve the controversy regarding the relationship between stress and ART treatment outcomes and the efficacy of psychoeducational interventions for patients participating in ART programs.

However, the results of this study are only applicable to women participating in an ART treatment program for the purposes of resolving infertility and achieving pregnancy. The extent to which these results apply to other populations has not be determined. Therefore, generalizations about the relationship between stress and fertility among normal women should not be made. Furthermore, the efficacy of psychoeducational interventions such as the application of the relaxation response in order to increase the likelihood of conception to women who have not been diagnosed with infertility cannot be determined. Finally, while this study will examine the relationship between stress and ART treatment outcomes, it did not explore other factors, such as coping skills, on the success of ART treatment.

CHAPTER FOUR: RESULTS

Problem Statement

The role stress plays in infertility and infertility treatment has been a common topic of research in the area of reproductive health and medicine. Historically, researchers have focused on whether stress caused infertility. While empirical research has not provided any evidence of this causal relationship, recent researchers have renewed this focus through the modification of the psychogenic hypothesis. While evidence establishing a causal relationship between stress and infertility is yet to be provided, the literature is replete with evidence documenting the stress caused by infertility and infertility treatment. Because of the salient and individualistic properties of stress, research has demonstrated that while general cyclical patterns of emotional reactions to the stress of infertility are present, every individual responds to the stress of infertility in varying degrees and may progress through the various stages of emotion in varying sequences. Most recent research focuses on the affect stress may have on the success of infertility treatment. However, results of these studies are varied leaving this issue to debate among researchers and physicians. Additionally, evidence regarding psychoeducational interventions in mitigating the impact of stress on the success of infertility treatment is in its' infancy. While mounting evidence suggests that psychoeducational interventions may be an

effective method addressing the emotional needs of infertility patients, a synthesis of accumulated data examining the relationship between stress and infertility treatment outcomes as well as the mitigating properties of psychoeducational interventions on infertility treatment success was nonexistent until the conduct of this study.

Research Purpose and Questions

Although not an epidemic, infertility is a significant health problem affecting millions of American couples. The role of stress on infertility and infertility treatment outcomes is complex, often leading researchers to conflicting conclusions. The purpose of this study was to investigate the impact of stress on the success of Assisted Reproductive Technology (ART) treatment outcomes. In addition, this study sought to determine whether psychoeducational interventions mitigate the impact of stress during ART treatments. Therefore, this study addresses two questions through a synthesis of the existing research:

1. Do increased levels of stress reduce the likelihood of ART treatment success?

2. Do psychoeducational interventions provided to patients participating in infertility treatment mitigate the effects of stress during ART treatment?

Collection and Evaluation of Studies

Literature Review

After identification of the research questions, studies to be included in the meta-analysis must be identified. Therefore, an exhaustive search of the literature was conducted in an effort to identify every primary research study conducted. Studies to be included in this meta-analysis were identified through the following methods:

- A comprehensive search of the English language literature from January 1985 through December 2003 through electronic database searches including MEDLINE/PubMed, ERIC, Psychinfo, and Dissertation Abstracts Online;

- Electronic branching from identified research studies located through the database searches;

- Manual scans of primary research studies identified;

- Contacting professionals active in conducting research in this field;

- A search all clinical trials completed; and

- A search of published abstracts from professional conferences including the American Society of Reproductive Medicine.

The results of this comprehensive search produced a total of 419 published articles, 1 conference abstract and 3 doctoral dissertations focusing on the relationship between stress and ART treatment outcomes, hypothesis one. Contact with Alice Domar, Jackie Boivin and Pauline Slade identified an

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additional 8 studies. The abstracts of each study and article were then read to identify those studies that examined the relationship between stress and ART treatment outcomes on at least one outcome measure. Of the initial pool of studies and articles located, 32 publications, one conference abstract and two dissertations were empirical investigations reporting research study results.

The search method for hypothesis two used the same searching methods described above, locating a total of 62 published studies and one dissertation focusing on the efficacy of psychoeducational interventions in mitigating the infertility stress experienced. Among these studies initially located, 21 studies and one dissertation reported the results of primary, empirical investigations.

Identification of Studies for Inclusion in the Meta-Analysis

In order to reduce selection bias and increase internal validity, this researcher reviewed each article identified presenting empirical data in the literature review. The purpose of this review was to ensure all articles and studies meeting specified criteria for inclusion in the meta-analysis were identified. For each hypothesis, each study met all of the following inclusion criteria:

1. For hypothesis one, the studies involved women participating in an ART treatment program. The focus of these studies was on the relationship between stress and ART treatment outcomes. For hypothesis two, the study involved women participating in a psychoeducational intervention program and an ART treatment

program. In addition, the study focused on the relationship between the psychoeducational intervention and stress.

2. The studies were conducted between January 1985 and December 2003.

3. The design of the study was prospective.

4. The studies reported outcome measures of stress or anxiety and treatment outcomes. For hypothesis one, treatment outcome was defined as achieving pregnancy or failure to achieve pregnancy. For hypothesis two, treatment outcome was defined as the post-treatment score. Studies with insufficient data for effect size calculations were excluded.

Among the 35 empirical studies located examining the relationship between stress and ART treatment outcomes, a total of 13 (37%) met the criteria for inclusion while the remaining 22 studies (Appendix F) were excluded from the meta-analysis for the following reasons:

1. Three (14%) included women in the sample that were participating in other types of infertility treatment such as Artificial Insemination and Intra-Uterine Insemination;

2. Eleven (50%) did not focus on the relationship between stress and ART treatment outcomes;

3. One (5%) was retrospective in design;

4. Six (27%) reported insufficient data or statistical analysis; and

5. One (5%) study was a copywriter-protected dissertation and was

    unobtainable.

Of these 13 studies included in the meta-analysis for hypothesis one, two

(15.38%) were conducted in Australia, three (23.08%) in Asia and the Middle

East (Southeast Asia), seven (53.85%) in Europe, and one (7.69%) in North

America. Data regarding the characteristics of the sample included in each study

were collected. Table 4 below depicts the number and percentage of studies

reporting sufficient information for describing the participants included in the

meta-analysis and for coding study characteristics as described in Appendix E.

Table 4

Studies reporting characteristics of sample for

hypothesis one

Characteristic	N	%
Age	11	84.46
Education	3	23.08
Employment	3	23.08
Economic Status	1	7.69
Classification	3	23.08
Etiology	11	84.46
Duration of Infertility	8	61.54
Type of ART	13	100.00
Number of Previous ART Attempts	4	30.77

Descriptive information for the female participants included in the meta-analysis

is presented in Table 5.

Table 5

Demographic information for studies reporting the effects of stress on

ART treatment outcomes

Characteristic	N	$\overline{X}$ (± SD)	%
Overall Sample Size	1348	103.69 (± 80.99)	
Overall Age	1195	32.99 (± 1.21)	
Employment Status			
Unknown	723		53.64
Not Employed	163		12.09
Employed	462		34.27
Classification of Infertility			
Unknown	1001		74.26
Primary	304		22.55
Secondary	43		3.19
Etiology			
Unknown	178		13.20
Female Factor Only	22		1.63
Male Factor Only	0		0
Combination	1148		85.16
Duration of Infertility	1117	5.39 (± 1.17)	
Type of ART			
IVF	1165		86.42
IVF or ICSI	127		9.42
IVF of GIFT	56		4.15
Previous ART Attempts			
Unknown	935		69.36
0	268		19.88
1 or 2	138		10.24
3 or More	41		3.04

Among the 22 empirical studies located examining the effects of

psychoeducational interventions on the stress experienced by women

participating in an ART program, a total of 4 (18%) studies met the inclusion

criteria for hypothesis two. Of the 22 studies reporting empirical data for

hypothesis two, a total of 18 were excluded from the meta-analysis for the

following reasons:

1. Twelve (55%) focused on women diagnosed with infertility, but not

    participating in an ART treatment program or participating in other

    types of treatment programs such as Intra-Uterine Insemination;

2. One (5%) focused on men only;

3. Four (18%) focused on outcome measures other than the impact on

    stress; and

4. One (5%) was retrospective in design.

Of these four studies included in the meta-analysis for hypothesis two, one

(25%) was conducted in Asia, two (50%) in Europe, and one (25%) in North

America. Data regarding the characteristics of the sample included in each study

were collected. Table 6 below depicts the number and percentage of studies

reporting sufficient information for describing the participants included in the

meta-analysis and for coding study characteristics as described in Appendix E.

Table 6

Studies reporting characteristics of sample for hypothesis two

Characteristic	N	%
Age	3	75.0
Education	1	25.0
Employment	1	25.0
Economic Status	2	50.0
Classification	1	25.0
Etiology	1	25.0
Duration of Infertility	4	100.0
Type of ART	3	75.0
Number of Previous ART Attempts	2	50.0

Descriptive information for the female participants included in part two of the meta-analysis is presented in Table 7.

Table 7

Demographic information for studies reporting the effects of psychoeducational interventions on stress experienced by women participating in an ART treatment program

Characteristic	N	$\overline{X}$ (± SD)	%
Overall Sample Size	498	124 (± 90.94)	
Treatment Group Sample Size	203	50.75 (± 39.76)	
Control Group Sample Size	225	56.25 (± 50.96)	
Overall Age	369	33.47 (± 1.29)	
Employment Status			
Unknown	438		88.0
Not Employed	25		5.0
Employed	35		7.0
Classification of Infertility			
Unknown	346		69.5
Primary	89		17.9
Secondary	63		12.7

Continued on the next page

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Table 7 (Continued)

Etiology			
Unknown	397		79.7
Female Factor Only	57		11.5
Male Factor Only	26		5.2
Combination	18		3.6
Duration of Infertility	369	4.98 (± 1.04)	
Type of ART			
IVF	498		100.0
IVF or ICSI			
IVF of GIFT			
Previous ART Attempts			
Unknown	257		51.6
0	241		48.4
1 or 2			
3 or More			
Psychoeducational Intervention			
Counseling	177		87.2
Support Group			
Cognitive Behavioral Format	26		12.8
Other			
Frequency of Psychoeducational Intervention			
1 – 3 sessions	147		72.4
4 – 5 sessions	30		14.8
Other	26		12.8
Length of Psychoeducational Intervention			
Unknown	110		54.2
1 hour	37		18.2
1.5 hours	26		12.8
2 hours			
Other	30		14.8

The final sample to be included in the meta-analysis consisted of a total of 13 studies meeting the inclusion criteria for hypothesis one and four studies meeting the inclusion criteria for hypothesis two (Appendix F).

Coding the Characteristics of Included Studies

Once all relevant studies were retrieved, the researcher determined the characteristics of interest within the studies. Conventions for coding these characteristics were developed. Finally, coding forms capturing the characteristics present in each study were then constructed. The purpose of coding study characteristics was to ensure the reliable and orderly extraction of information from each of the studies. For this study, characteristics reviewed and coded are presented in Appendix C, while the coding sheet appears in Appendix D and the coding manual and reference guide appears in Appendix E.

In addition to coding the characteristics of interest, the quality of each study was reviewed. This review applied the validity framework developed by Campbell and his associates (Wortman, 1994), providing a matrix of design and study features. This structured review of each study's quality for this meta-analysis appears in Appendix B and was included in the coding process for each study. Based on the responses, a score of each study's quality index was generated. Each question was scored as 1 for yes responses and 0 for no responses. The quality index score was determined as follows:

1. Each category was summed and averaged and

2. The average scores from each category were averaged.

A pilot test of the master coding sheet, developed by this researcher, capturing the relevant study characteristics as well as the quality characteristics was conducted. Two professional evaluators meeting the following qualifications were recruited to participate:

- Completed a Doctor of Philosophy degree in Measurement and Research and

- Current professional in the field of research and evaluation.

Training and implementation of the coding process were as follows: First, the two independent evaluators were furnished with a copy of a coder training manual and reference guide. Each coder used the manual and reference guide to code a single article independently. Next, the researcher met with each evaluator independently to discuss problems encountered in using the guide and the coding sheet, and to make any adjustments or changes to the guide, the coding sheet, or both as required. The two evaluators were then assigned to a random sample of all of the articles to code for each hypothesis. For hypothesis one, each evaluator received the same six articles to code. For hypothesis two, each evaluator received the same two articles to code. The code sheets submitted by the two evaluators were then compared to the master code sheet developed by the researcher. Items scored differently by either the researcher or by the two independent evaluators were discussed by the team. Item scores in disagreement were coded by majority decision between the three evaluators. Interrater agreement was assessed by comparing the values recorded by each coder for each of the variables of interest. Raters were in agreement if all coders recorded identical values. The level of agreement obtained for the variables is presented in Table 8. As these results indicate, the level of agreement was reasonably high with a mean overall agreement of 94.09%.

Table 8

Study coding agreement

Coding Sections	% Agreement
Part I – Study Characteristics	98.00
Publication Characteristics	100.00
Ecological Characteristics	97.92
Methodological Characteristics	96.67
Results	100.00
Part II – Quality	92.65
Design	95.00
Participants	93.94
Controls/Implementation	91.67
Protocol	93.33
Outcomes	91.67
Statistics	83.33
Total Instrument	94.09

Findings

Hypothesis One

The effect size metric computed for each study was Cohen's *d*,

$$d_i = \frac{\overline{X}_i^1 - \overline{X}_i^2}{s_i}$$

where

$\overline{X}_i^1 =$ the mean of group 1 in the *i*th study,

$\overline{X}_i^2 =$ the mean of group 2 in the *i*th study, and

$s_i =$ the pooled standard deviation of the two groups,

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providing a common scale for comparison of study outcomes. When a study

reported multiple measures of stress that represented the same construct, for the

same sample group in a study, Cohen's effect sizes were calculated for each

measure and then averaged and weighted to provide one statistic for each study.

When a study reported multiple measures of stress representing different

constructs as defined in Appendix G, an effect size estimate was computed for

each construct. Finally, for studies providing outcome measures at multiple

points during the treatment program, an effect size estimate was computed for

each point measured. Table 9 lists the information extracted from each study as

well as the index of effect size and 95% Confidence Interval while Appendix H

provides the SAS code.

Table 9

Studies reporting the effects of stress as it relates to ART treatment outcomes

Study	N	Country	$\overline{X}$ Age	Etiology [a]	$\overline{X}$ Duration	Time[b]	Constru ct[c]	d	95% CI	
									Lower	Upper
Gallinelli et al. (2001)	40	Italy		1		3	1	0.459	-0.2423	1.1603
Gallinelli et al. (2001)	40	Italy		1		3	2	0.080	-0.6143	0.7743
Biovin & Takefman (1995)	40	Canada	33.3	0	4.4 years	1	1	-0.071	-0.6981	0.5561
Biovin & Takefman (1995)	40	Canada	33.3	0	4.4 years	2	1	0.573	-0.0664	1.2123
Biovin & Takefman (1995)	40	Canada	33.3	0	4.4 years	3	1	0.806	0.1547	1.4573
Biovin & Takefman (1995)	40	Canada	33.3	0	4.4 years	4	1	0.643	0.0005	1.2855
Biovin & Takefman (1995)	40	Canada	33.3	0	4.4 years	5	1	0.866	0.2110	1.5210
Biovin & Takefman (1995)	40	Canada	33.3	0	4.4 years	1	2	0.190	-0.4383	0.8183
Kee et al. (2000)	138	Korea	32.8	0	5.5 years	1	1	1.412	0.0395	1.0225
Kee et al. (2000)	138	Korea	32.8	0	5.5 years	1	2	1.787	1.3766	2.1974
Kee et al. (2000)	138	Korea	32.8	0	5.5 years	1	3	0.949	0.5796	1.3184
Thiering et al. (1992)	312	Australia	33.7	1		1	1	-0.630	-0.8869	-0.3731
Thiering et al. (1992)	312	Australia	33.7	1		1	2	-0.061	-0.3131	0.1911
Thiering et al. (1992)	312	Australia	33.7	1		1	3	-0.117	-0.3693	0.1353

Continued on the next page

Table 9 (Continued)

Study	n	Country	Age	Etiology[a]	Duration	Time[b]	Construct[c]	ES	Lower	Upper
Verhaak et al. (2001)	127	Netherlands	33.4	1	3.7 years	1	1	0.199	-0.1788	0.5768
Verhaak et al. (2001)	127	Netherlands	33.4	1	3.7 years	1	3	0.326	-0.0532	0.7052
Ardenti et al. (1999)	200	Italy	33.8	1	6.1 years	3	1	-0.616	-0.9744	-0.2576
Ardenti et al. (1999)	200	Italy	33.8	1	6.1 years	3	2	0.034	-0.3193	0.3873
Sanders & Bruce (1999)	56	Australia	32.6	1		1	1	0.498	-0.0392	1.0352
Sanders & Bruce (1999)	56	Australia	32.6	1		1	2	0.579	0.0390	1.1190
Csemiczky et al. (2000)	22	Sweden	33.4	2		1	1	0.856	-0.0225	1.7525
Csemiczky et al. (2000)	22	Sweden	33.4	2		2	1	0.598	-0.2701	1.4661
Csemiczky et al. (2000)	22	Sweden	33.4	2		5	1	1.528	0.5656	2.4904
Facchinetti et al. (1997)	49	Italy	33.9	1	6.3 years	1	1	0.241	-0.3580	0.8400
Facchinetti et al. (1997)	49	Italy	33.9	1	6.3 years	3	1	0.437	-0.1663	1.0403
Facchinetti et al. (1997)	49	Italy	33.9	1	6.3 years	1	2	0.629	0.0191	1.2389
Demyttenaere et al. (1993)	40	Belgium	32.4	1	6.1 years	2	1	0.473	-0.2502	1.1962
Demyttenaere et al. (1993)	40	Belgium	32.4	1	6.1 years	3	1	0.190	-0.5269	0.9069
Demyttenaere et al. (1993)	40	Belgium	32.4	1	6.1 years	4	1	0.000	-0.7157	0.7157
Demyttenaere et al. (1993)	40	Belgium	32.4	1	6.1 years	2	3	2.723	1.7912	3.6548
Merari et al. (1992)	113	Israel				2	1	-0.212	-0.6708	0.2468
Merari et al. (1992)	113	Israel				3	1	-0.177	-0.6355	0.2815
Merari et al. (1992)	113	Israel				4	1	0.065	-0.3930	0.5230
Merari et al. (1992)	113	Israel				5	1	0.107	-0.3512	0.5652
Merari et al. (1992)	113	Israel				1	3	0.048	-0.4100	0.5060
Merari et al. (1992)	113	Israel				2	3	-0.328	-0.7879	0.1319
Merari et al. (1992)	113	Israel				3	3	-0.306	-0.7657	0.1537
Merari et al. (1992)	113	Israel				4	3	0.067	-0.3910	0.5250
Merari et al. (1992)	113	Israel				5	3	-0.007	-0.4649	0.4509
Demyttenaere et al. (1998)	98	Belgium	29.7	1	4.1 years	1	3	0.041	-0.4262	0.5082
Merari et al. (1996)	113	Israel	33.9	1	6.9 years	1	1	0.024	-0.4340	0.4820
Merari et al. (1996)	113	Israel	33.9	1	6.9 years	1	2	0.050	-0.4080	0.5080
Merari et al. (1996)	113	Israel	33.9	1	6.9 years	1	3	-0.332	-0.7920	0.1280

[a] Etiology is coded as follows: 0 = Unknown, 1 = Mixed (combination of female factor and male factor),   2 = Female factor only

[b] Time is coded as follows to reflect the time the measure was administered: 1 = Baseline/Pre-Treatment,   2 = Follicular Phase (day 3 – day 14),

   3 = Oocyte Retrieval, 4 = Embryo Transfer, 5 = Luteal Phase (approximately days 21 – 28)

[c] Construct is coded to reflect the construct of the measure as defined in Appendix G: 1 = Acute Stress, 2 = Chronic Stress, and 3 = Depression.

Note. Effect sizes are scored so that positive numbers reflect greater amounts of stress in the group who failed to become pregnant and negative numbers reflect greater amounts of stress in the group who achieved pregnancy.

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Figure 1 displays the 13 studies included in the meta-analysis for hypothesis one

listed in Table 9, rank ordered by the magnitude of the effect size by the time at

which the measure was administered and the construct for which the measure

reports. As illustrated in Figure 1, results across primary studies vary greatly.

Among studies reporting acute stress measures at the time of baseline/pre-

treatment, effect size estimates ranged from –0.630 to 1.412 with a mean of

0.290. Likewise, similar findings are shown in primary studies reporting acute

stress measures during the follicular phase (range= -0.212 to 0.598, $\bar{X}$ = 0.2579)

and at oocyte retrieval (range= -0.616 to 0.806, $\bar{X}$ =0.1052) while measures of

acute stress at the time of embryo transfer (range= 0 to 0.643, $\bar{X}$ = 0.1977) and

during the luteal phase (range= 0.107 to 1.528, $\bar{X}$ = 0.7031) were all positive.

Among primary studies reporting chronic stress measures, results varied.

Baseline/pre-treatment chronic stress measures ranged from –0.061 to 1.787

with a mean of 0.4491 while chronic stress measures taken at the time of oocyte

retrieval ranged from 0.034 to 0.08 with a mean of –0.1874. Finally, measures of

depression demonstrated a large amount of variability across studies as well.

Measures of depression reported for baseline/pre-treatment and follicular phase

end-points ranged from negative to positive effect size estimates (range= 0.332

to 0.949, $\bar{X}$ = 0.1702; range= -0.328 to 2.723, $\bar{X}$ = 1.0629, respectively).

Figure 1.

Dot plot for studies reporting the effects of stress on ART treatment outcomes
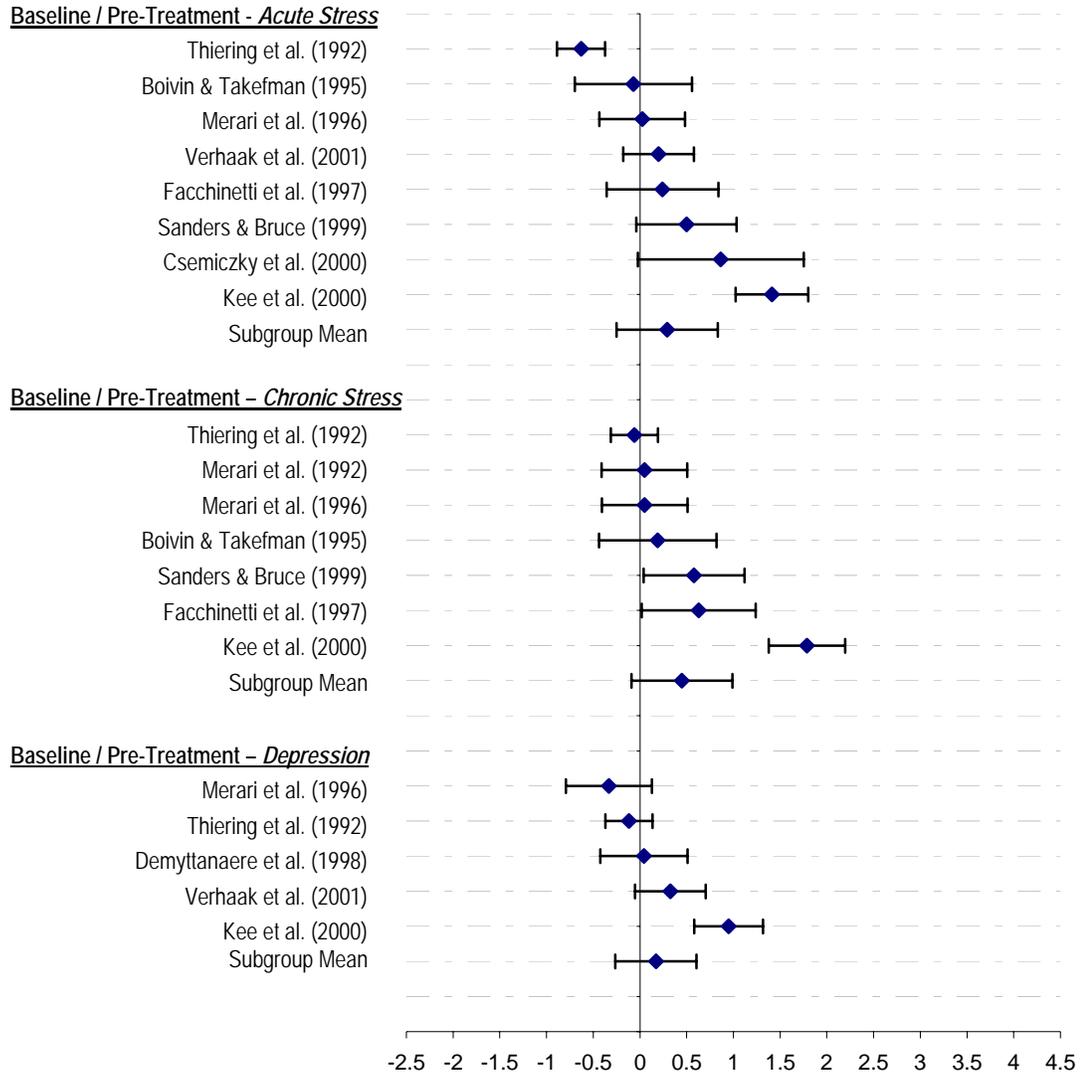
180
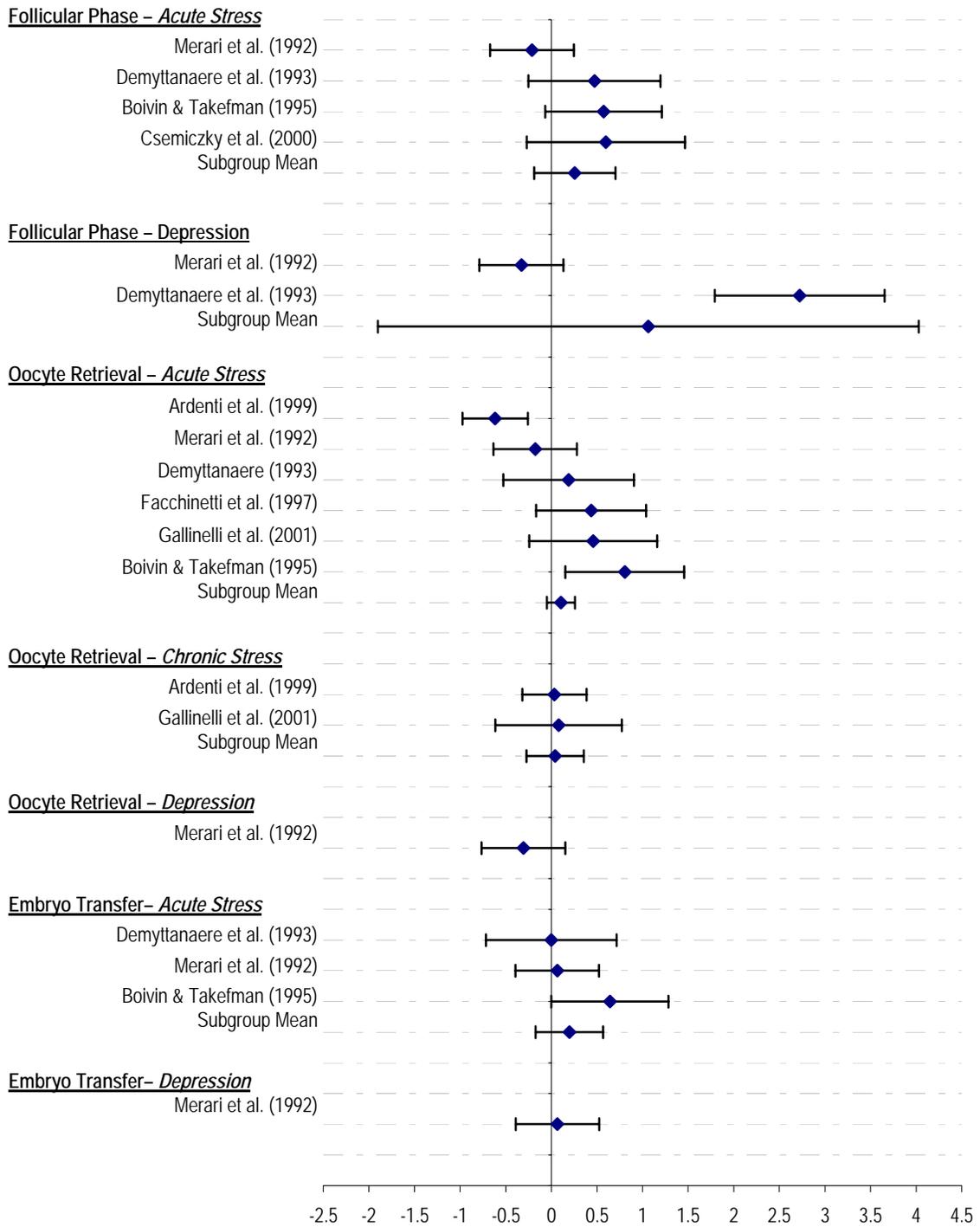
Figure 1 (Continued)

Figure 1 continued
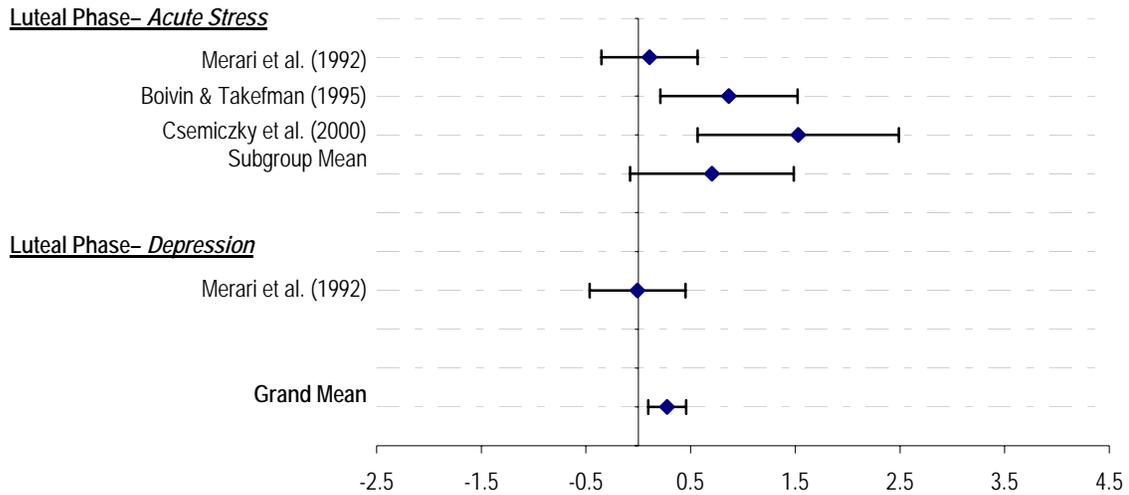
To test data for outliers, the Sample-Adjusted Meta-Analytic Deviancy (SAMD) statistic was computed using SAS 8.2. Programming code for this analysis appears in Appendix I while the results are displayed in Table 10. In addition, scree plots were constructed to visually identify outliers and are presented in Appendix J. Effect sizes with a SAMD statistic greater than 3.0 were considered extreme observations.

Table 10

Test for outliers among effect sizes for studies reporting the effects of stress on ART treatment

Time	Construct	Study	d	SAMD
Baseline/Pre-treatment	Acute Stress	Kee et al. (2000)	1.412	7.77
		Thiering et al. (1992)	-0.630	5.44
		Csemiczky et al. (2000)	0.865	1.88
		Sanders & Bruce (1999)	0.498	1.73
		Verhaak et al. (2001)	0.199	0.97
		Facchinetti et al. (1997)	0.241	0.75
		Boivin & Takefman (1995)	-0.071	0.27
		Merari et al. (1996)	0.024	0.02

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Table 10 (Continued)

	Chronic Stress	Kee et al. (2000)	1.787	9.53
		Facchinetti et al. (1997)	0.629	1.91
		Sanders & Bruce (1999)	0.579	1.86
		Thiering et al. (1992)	-0.061	1.24
		Boivin & Takefman (1995)	0.190	0.39
		Merari et al. (1992)	0.048	0.11
		Merari et al. (1996)	0.050	0.10
	Depression	Kee et al. (2000)	0.949	5.14
		Merari et al. (1996)	-0.332	1.84
		Verhaak et al. (2001)	0.326	1.59
		Thiering et al. (1992)	-0.117	1.32
		Demyttenaere et al. (1998)	0.041	0.05
Follicular Phase	Acute Stress	Boivin & Takefman (1995)	0.573	1.58
		Merari et al. (1992)	-0.212	1.39
		Demyttenaere et al. (1993)	0.473	1.27
		Csemiczky et al. (2000)	0.598	1.22
	Chronic Stress	Demyttenaere et al. (1993)	2.723	7.63
		Merari et al. (1992)	-0.328	2.26
Oocyte Retrieval	Acute Stress	Ardenti et al. (1999)	-0.616	3.91
		Boivin & Takefman (1995)	0.806	2.47
		Facchinetti et al. (1997)	0.437	1.50
		Gallinelli et al. (2001)	0.459	1.42
		Merari et al. (1992)	-0.177	0.82
		Demyttenaere et al. (1993)	0.190	0.60
	Chronic Stress	Gallinelli et al. (2001)	0.080	0.21
		Ardenti et al. (1999)	0.034	0.09
Embryo Transfer	Acute Stress	Boivin & Takefman (1995)	0.643	1.60
		Merari et al. (1992)	0.065	0.66
		Demyttenaere et al. (1993)	0.000	0.31
Luteal Phase		Csemiczky et al. (2000)	1.528	3.09
		Boivin & Takefman (1995)	0.866	2.25
		Merari et al. (1992)	0.107	0.44

The following five studies were identified as outliers:

1. Kee et al. (2000)

2. Thiering et al. (1992)

3. Demyttenaere et al. (1993)

4. Ardenti et al. (1999)

5. Csemiczky et al. (2000).

These studies were reviewed to determine if there were any identifiable

characteristics in the populations or conditions that may account for the

differences observed. While there were no clear or obvious differences in the

sample population or conditions in the study reported by Thiering et al. (1992),

three of the studies did have characteristics unique to their populations or

conditions. The study conducted by Kee et al. (2000) was the only study

completed in Asia, specifically South Korea. More notably, in the introduction of

the study, it was stated

In the past, traditionally if Korean women were infertile, they were

regarded as having one of the "seven largest sins." Thus, they were

stressed from the mistreatment at the hands of their own family members.

This historical cultural or religious difference may have contributed to the extreme

effect sizes observed. In the study conducted by Ardenti et al. (1999) the focus

was specifically on stress measures taken at the time of oocyte retrieval and

embryo transfer. However, unlike any of the other studies included in the meta-

analysis, it was reported that the women were hospitalized during these stages of

the treatment. In addition, the mean duration of knowledge of their infertility for

this sample was reportedly 6.1 years, ranging from 1 to 22 years. While this

mean duration is not the highest reported average, the range reported was the

largest. Similarly, the study conducted by Demyttenaere et al. (1993) reported a

mean duration of infertility of 6.1 years (± 3.1). Finally, in the study conducted by

Csemiczky et al. (2000), unlike the other studies included in the meta-analysis, it

was noted that the participants in the study had been on a waiting list to receive

treatment for an average of 4.3 years.

Next, a homogeneity test was conducted to determine whether the sample

effect sizes for the 28 data points in the meta-analysis were homogenous. SAS

8.2 was used to perform the homogeneity test (see Appendix I). As shown in

Table 11, the Q-statistic for measures of depression at baseline/pre-treatment,

acute stress at oocyte retrieval, and acute stress at the luteal phase were

significant at the .05 level, indicating that effect sizes are not homogeneous.

Table 11

Test of homogeneity of effect sizes including outliers for hypothesis one

Source	df	Q-Stat	p
Baseline –Acute Stress	7	80.4367	>0.0001
Baseline – Chronic Stress	6	62.3665	>0.0001
Baseline - Depression	4	27.5261	0.00002
Follicular Phase – Acute Stress	3	5.7607	0.12385
Follicular Phase – Depression	1	33.1169	>0.0001
Oocyte Retrieval – Acute Stress	5	21.4644	0.00066
Oocyte Retrieval – Chronic Stress	1	0.0134	0.90786
Embryo Transfer – Acute Stress	2	2.4592	0.29241
Luteal Phase – Acute Stress	2	8.4055	0.01495

A test of homogeneity was also conducted excluding the outliers identified with

the SAMD statistic. Excluding the extreme observations, the Q-statistic was not

significant at the .05 level for any of the measures as shown in Table 12

suggesting that the data are homogenous.

Table 12

Test of homogeneity of effect sizes excluding outliers for hypothesis one

Source	df	Q-Stat	p
Baseline –Acute Stress	5	4.6051	0.46594
Baseline – Chronic Stress	5	7.6442	0.17696
Baseline - Depression	3	5.5882	0.13346
Follicular Phase – Acute Stress	3	5.7607	0.12385
Oocyte Retrieval – Acute Stress	4	4.6051	0.14317
Oocyte Retrieval – Chronic Stress	1	0.0134	0.90786
Embryo Transfer – Acute Stress	2	2.4592	0.29241
Luteal Phase – Acute Stress	1	3.4638	0.06273

A funnel plot investigating the properties of the effect sizes for the studies included in the meta-analysis was also constructed. Figure 11 displays these results. The shape of the funnel plot indicates the presence of publication bias. In other words, it appears that studies with smaller sample sizes reporting a negative effect, indicating that participants experiencing greater levels of stress were more likely to become pregnant following ART treatment, were not published.

Figure 11.

Funnel plot for studies reporting the effects of stress on ART treatment outcomes
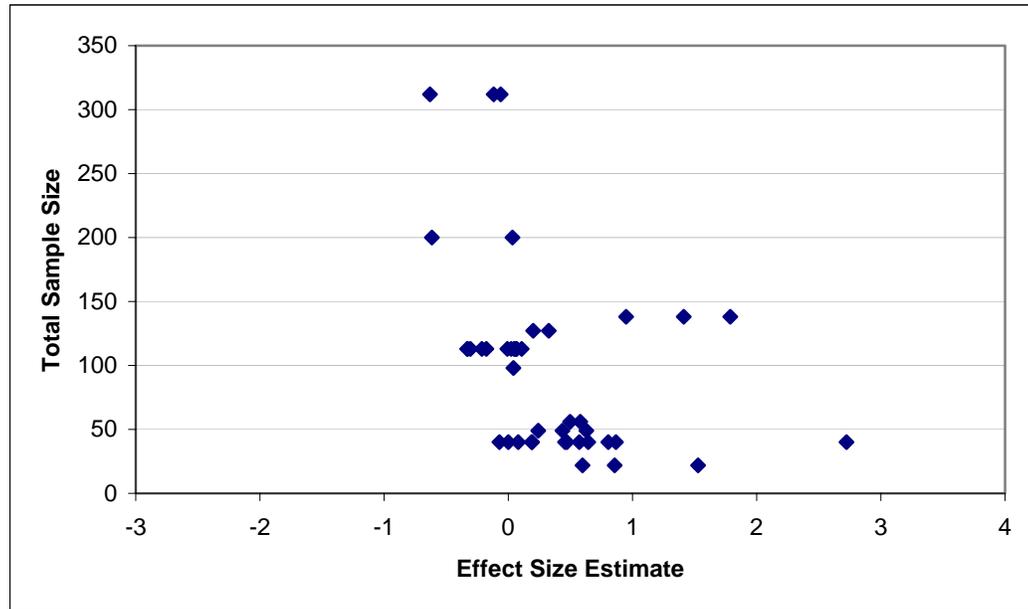
Finally, a regression analysis was conducted to statistically analyze the effect-size estimates. Two hypothesis tests were conducted. First, the null hypothesis for the regression coefficient β_q for any q = 0, …., p is as follows:

$$H_0 : \beta_q = 0.$$

The regression coefficients represent the variables time (baseline/pre-treatment, follicular phase, oocyte retrieval, and embryo transfer) and construct (acute stress and chronic stress). In this model, predictors are coded with depression measures taken during the luteal phase as reference categories. Results including outliers and excluding outliers are presented in Table 13. Although the results including study outliers at each time measured demonstrate a small to moderate negative relationship between stress and ART treatment outcome

(ranging from –0.1832 at the time of embryo transfer to –0.5037 at the time of baseline/pre-treatment), none of these coefficients are statistically significant. Similar results are found for the construct acute stress (-0.0839) demonstrating a small negative effect with ART treatment outcome while chronic stress (0.2682) demonstrates a small positive relationship with ART treatment outcomes. Again, neither acute stress nor chronic stress was statistically significant. When study outliers are excluded, the intercept demonstrates a small relationship with ART treatment outcomes and is still statistically significant. In addition, the effect size estimates for time (baseline/pre-treatment, follicular phase, oocyte retrieval and embryo transfer) show a small to moderate negative effect on ART treatment outcome, but are not statistically significant. Furthermore, acute stress and chronic stress demonstrated a small to moderate positive effect on ART treatment outcome. However, neither of these coefficients was statistically significant.

Table 13

Hierarchical random effects analysis for hypothesis one

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI		Estimate	p-value	95% CI	
			Lower	Upper			Lower	Upper
Intercept	0.7040	0.0280	0.09014	1.31790	0.36360	0.0438	0.01205	0.71510
Baseline / Pre-treatment	-0.5037	0.0757	-1.06360	0.05625	-0.30100	0.0689	-0.62790	0.02592
Follicular Phase	-0.2081	0.4431	-0.75910	0.34280	-0.25450	0.1111	-0.57360	0.06462
Oocyte Retrieval	-0.4211	0.1193	-0.95900	0.11690	-0.26550	0.0868	-0.57350	0.04248
Embryo Transfer	-0.1832	0.5125	-0.75210	0.38560	-0.08916	0.5697	-0.41260	0.23430
Acute Stress	-0.0839	0.5174	-0.34740	0.17960	0.13190	0.1402	-0.04770	0.31160
Chronic Stress	0.2682	0.1514	-0.04441	0.58070	0.14070	0.1431	-0.05238	0.33390

Note. A total of 13 studies representing 43 effect sizes were included in the analysis including outliers. A total of 12 studies representing 36 effect sizes were included in the analysis excluding outliers.

The null hypothesis for the random effects variance:

$$H_0 : \sigma^2_\theta = 0 .$$

was tested. This hypothesis was tested by computing a weighted least squares

regression with weights equal to $w_i = \dfrac{1}{v_i}$. The weighted residual sum of

squares was compared with the critical values of chi-square distribution with k –

p – 1 degrees of freedom. As shown in Table 14, both the intercept and residual

variance estimates are significant at the .05 level for results including outliers

while only the residual variance estimate was significant for results excluding

outliers.

Table 14

Heirarchical random effects variance analysis for hypothesis one

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI[a]		Estimate	p-value	95% CI[a]	
			Lower	Upper			Lower	Upper
Intercept	0.23640	0.0200	0.10970	0.82910	0.05229	0.0507	0.02089	0.28810
Residual	1.91040	0.0002	1.18080	3.60900	0.57280	0.0012	0.32940	1.23570

[a]Due to different formulas used in the inferential statistics reported above, the 95% CI results may conflict with the significance
test. The results provided by the significance test are considered to be reliable for interpretation.
Note. A total of 13 studies representing 43 effect sizes were included in the analysis including outliers. A
total of 12 studies representing 36 effect sizes were included in the analysis excluding outliers.

SAS code for computing the coefficients and conducting the analysis is listed in

Appendix K.

Since the variables time (baseline/pre-treatment, follicular phase, oocyte

retrieval, and embryo transfer) and construct (acute stress and chronic stress)

did not significantly contribute to the model, a null model including outliers and

excluding outliers was constructed. SAS code is presented in Appendix L.

Results of this analysis found that the intercept was not statistically significant

when study outliers were included. However, when outliers were removed from

the analysis, results indicate that stress has a small effect on ART treatment

outcome with an estimated mean effect size of 0.2012 and is statistically

significant (see Table 15).

Table 15

Hierarchical random effects null model analysis for hypothesis one

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI		Estimate	p-value	95% CI	
			Lower	Upper			Lower	Upper
Intercept	0.30470	0.0541	-0.00635	0.61570	0.20120	0.0252	0.03007	0.37240

Note. A total of 13 studies representing 43 effect sizes were included in the analysis including outliers. A total of 12 studies representing 36 effect sizes were included in the analysis excluding outliers.

In addition, the analysis of the variance estimates including outliers as well as

excluding outliers reveal statistically significant results as outlined in Table 16.

Table 16

Hierarchical random effects null model variance analysis for hypothesis one

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI[a]		Estimate	p-value	95% CI[a]	
			Lower	Upper			Lower	Upper
Intercept	0.20610	0.02000	0.09558	0.72310	0.05271	0.0403	0.02202	0.25080
Residual	2.17100	<0.0001	1.40180	3.80800	0.62790	0.0002	0.38560	1.20000

[a]Due to different formulas used in the inferential statistics reported above, the 95% CI results may conflict with the significance test. The results provided by the significance test are considered to be reliable for interpretation.

Note. A total of 13 studies representing 43 effect sizes were included in the analysis including outliers. A total of 12 studies representing 36 effect sizes were included in the analysis excluding outliers.

Finally, a moderator analysis was conducted to determine if either the duration of infertility for the study participants (Appendix M) or the country in which the study was conducted (Appendix N) contribute to the model. The analysis of the coefficient estimates are presented in Table 17 while the random effects variance analysis is presented in Table 18. None of the estimates for the variable duration of infertility were statistically significant regardless of whether study outliers were included or excluded in the analysis. When examining the variable country in which the study was conducted, when study outliers are included, the coefficient estimate for studies conducted South East Asia was statistically significant at the .05 level. However, when outliers are excluded from the analysis, results demonstrate that a small positive relationship between stress and ART treatment outcome is significant at the .05 level while none of the coefficients by country were statistically significant.

Table 17

Hierarchical random effects analysis of moderators for hypothesis one

Moderator	Parameter	Including Outliers				Excluding Outliers			
		Estimate	p-value	95% CI		Estimate	p-value	95% CI	
				Lower	Upper			Lower	Upper
Duration of Infertility									
	Intercept	0.83920	0.4023	-1.38700	3.06550	0.67950	0.1233	-0.24830	1.60740
	Duration	-0.08705	0.6135	-0.44680	0.27270	-0.08716	0.2276	-0.23730	0.06296
Country									
	Intercept	0.27130	0.1000	-0.06355	0.60620	0.25610	0.0175	0.05645	0.45580
	Australia	-0.24430	0.4170	-0.89400	0.40540	-0.09233	0.6076	-0.48490	0.30030
	North America	0.30380	0.3883	-0.40570	1.01330	0.31990	0.1139	-0.08274	0.72240
	South East Asia	1.08200	0.0160	0.25460	1.90940				
	South West Asia	-0.35480	0.2301	-0.97830	0.26870	-0.33970	0.0708	-0.71490	0.03551

Note. A total of 8 studies representing 24 effect sizes were included in the analysis including outliers for the variable duration of infertility. A total of 7 studies representing 19 effect sizes were included in the analysis excluding outliers for the variable duration of infertility.

Results of this analysis of the variance indicate that for duration of infertility, with outliers included in the analysis, both the intercept and residual variances are statistically significant. However, when study outliers are excluded from the analysis, only the residual variance estimate is statistically significant at the .05 level. A comparison of the residual variance of the variable duration of infertility with the null model residual variance estimates reveals that the duration of infertility does not contribute to the model or account for an increase in the amount of variability accounted for in the model. Therefore, it appears that the variable duration of infertility does not act as a moderating variable. In the analysis of variance investigating country in which the study was conducted as a possible moderator, only the residual variance is statistically significant for the analysis including study outliers and for the analysis excluding study outliers. When comparing the variance estimates to the null model, the addition of the variable country in which the study was conducted slightly reduces both the intercept and residual variance estimates suggesting that the country in which the study is conducted may contribute to accounting for slightly more of the variability in this model.

Table 18

Hierarchical random effects variance analysis of moderators for hypothesis one

Moderator	Parameter	Including Outliers				Excluding Outliers			
		Estimate	p-value	95% CI[a]		Estimate	p-value	95% CI[a]	
				Lower	Upper			Lower	Upper
Duration of Infertility[b]									
	Intercept	0.25790	0.0695	0.09575	1.85750	0.02917	0.1820	0.00727	2.26800
	Residual	2.95410	0.0019	1.65530	6.70360	0.77250	0.0065	0.40030	2.06890

Continued on the next page

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Table 10 (Continued)

Country[c]									
Intercept	0.08274	0.1202	0.02566	1.38160	0.03235	0.1113	0.01034	0.45770
Residual	2.22190	<0.0001	1.42310	3.95040	0.61070	0.0003	0.37120	1.18830

[a]Due to different formulas used in the inferential statistics reported above, the 95% CI results may conflict with the significance test. The results provided by the significance test are considered to be reliable for interpretation.

Note.[b]A total of 8 studies (24 effect sizes) contributed to the analysis including outliers and a total of 7 studies (19 effect sizes) contributed to the analysis excluding outliers for the variable duration of infertility. [c]A total of 13 studies (43 effect sizes) contributed to the analysis including outliers and a total of 12 studies (36 effect sizes) contributed to the analysis excluding outliers for the variable country.

In order to test for moderating effects of the variable duration of infertility, a subset of studies were used due to many studies missing information regarding the duration of infertility for the women included in the sample. Therefore, a null model was constructed using this subset of studies for comparison purposes with the analysis for the variable duration of infertility as a moderator. Table 19 presents the null model estimates for the intercept coefficient and Table 20 presents the results for the variance components. The results of this analysis show that the intercept is not statistically significant for the model including outliers as well as for the model excluding outliers. However, estimates for the residual variance component, are statistically significant for the model including outliers and for the model excluding outliers while the intercept variance estimate is not statistically significant for either model.

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Table 19

Hierarchical random effects null model analysis for studies reporting information on the duration of infertility for hypothesis one

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI[a]		Estimate	p-value	95% CI[a]	
			Lower	Upper			Lower	Upper
Intercept	0.36580	0.1024	-0.09467	0.82630	0.20730	0.0577	-0.00931	0.42390

[a]Due to different formulas used in the inferential statistics reported above, the 95% CI results may conflict with the significance test. The results provided by the significance test are considered to be reliable for interpretation.

Note. A total of 8 studies representing 24 effect sizes were included in the analysis including outliers for the variable duration of infertility. A total of 7 studies representing 19 effect sizes were included in the analysis excluding outliers for the variable duration of infertility.

Table 20

Hierarchical random effects null model variance analysis for studies reporting information on the duration of infertility for hypothesis one

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI		Estimate	p-value	95% CI	
			Lower	Upper			Lower	Upper
Intercept	0.23120	0.0619	0.08838	1.49220	0.03193	0.1385	0.00929	0.77780
Residual	2.92470	0.0018	1.64780	6.56570	0.78900	0.0053	0.41520	2.04250

Note. [a]A total of 8 studies representing 24 effect sizes were included in the analysis including outliers for the variable duration of infertility. A total of 7 studies representing 19 effect sizes were included in the analysis excluding outliers for the variable duration of infertility.

Hypothesis Two

The second part of this study investigated the relationship between psychoeducational interventions and the stress experienced by women participating in ART treatment regimens. Specifically, this investigation sought to answer the following question: Do psychoeducational interventions mitigate the distress experienced by patients participating in an Assisted Reproductive

Technology (ART) treatment regimen? The first step in analyzing the

relationship between psychoeducational interventions and stress was to compute

an effect size. The metric used for this analysis was Cohen's *d*, providing a

common scale for comparison of study outcomes. Table 21 lists the information

extracted from each study as well as the index of effect size and 95% Confidence

Interval.

Table 21

Studies reporting the effects of psychoeducational interventions as they relate to

stress experienced during ART treatment regimens

Study	N	Country	$\overline{X}$ Age	Etiology [a]	$\overline{X}$ Duration	PI [b]	Frequency [c]	Construct [d]	d	95% CI	
										Lower	Upper
Connolly et al. (1993)	152	United Kingdom	32	1	5.4 years	1	1	1	.38	-0.0605	0.8171
Connolly et al. (1993)	152	United Kingdom	32	1	5.4 years	1	1	3	1.16	0.6928	1.6328
Emery et al. (2003)	282	Switzerland	34.4	0	3.8 years	1	1	1			
Randomized	200								.32	-0.1729	0.8093
Non-Randomized	82								.26	0.0625	-0.2319
Emery et al. (2003)	282	Switzerland	34.4	0	3.8 years	1	1	2			
Randomized	200								-.28	-0.7723	0.2087
Non-Randomized	82								.19	-0.3039	0.6747
Emery et al. (2003)	282	Switzerland	34.4	0	3.8 years	1	1	3			
Randomized	200								.46	-0.0375	0.9503
Non-Randomized	82								.20	-0.2888	0.6900
McNaughton-Cassill et al. (2002)	45	North America	34	0	5.75 years	3	2	1	0.80	0.1820	1.4010
McNaughton-Cassill et al. (2002)	45	North America	34	0	5.75 years	3	2	3	0.10	-0.4955	0.6883
Terzioglu (2001)	90	Turkey		0		1	3	1	0.59	0.0771	1.1113
Terzioglu (2001)	90	Turkey		0		1	3	3	1.29	0.7367	1.8497

[a] Etiology is coded as follows: 0 = Unknown, 1 = Mixed (combination of female factor and male factor)

[b] Psychoeducational Intervention is coded as follows: 1=Counseling, 2=Support Group,3=Cognitive Behavioral Format

[c] Frequency is coded as follows: 1=1-3 sessions, 2=4-6 sessions, 3=Other

[d] Construct is coded as follows: 1=Acute Stress, 2=Chronic Stress, 3=Depression

Note. Effect sizes are scored so that positive numbers reflect smaller amounts of stress in the group who participated in a psychoeducational intervention.

Figure 12 displays the 4 studies included in the meta-analysis for hypothesis two listed in Table 21, rank ordered by the magnitude of the effect size by the construct for which the measure reports. As shown in Figure 12, all of the studies are positive for the constructs acute stress and depression. However, one of the studies demonstrates a small negative effect for the construct chronic stress. While the majority of studies had a small to moderate observed effect, two studies had a very large observed effect (1.29 and 1.16) for the construct depression.

Figure 12.

Dot plot for studies reporting the effects of psychoeducational interventions on stress during ART treatment regimens
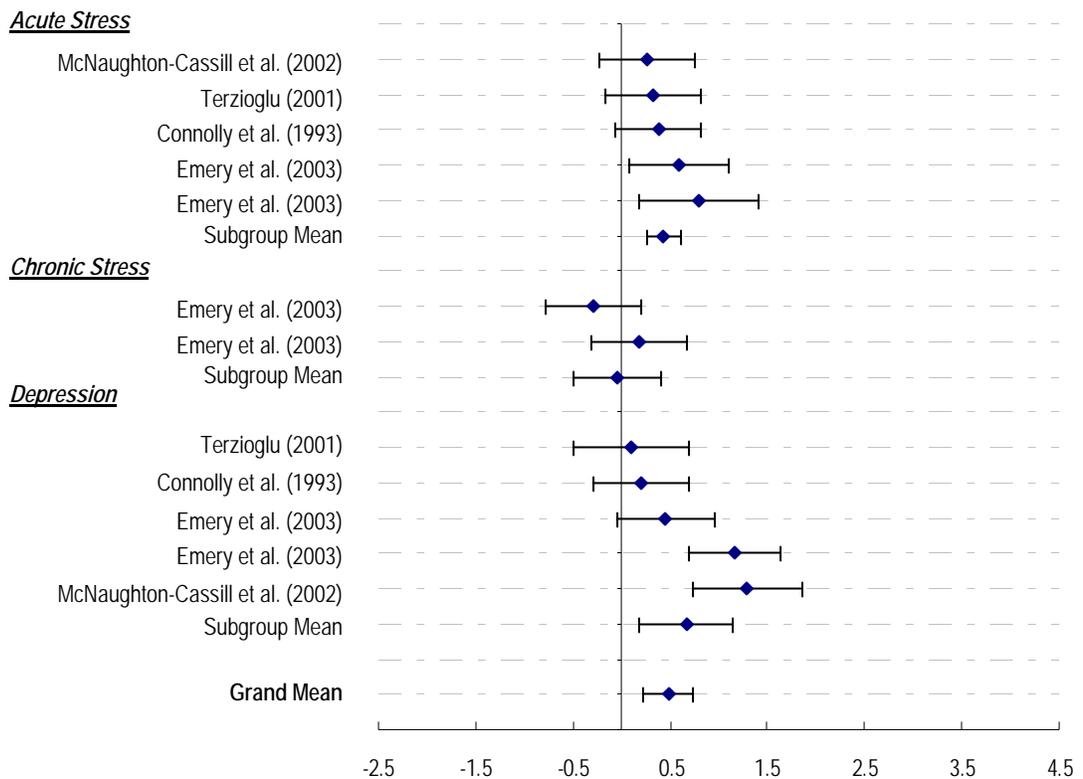
To test data for outliers, the Sample-Adjusted Meta-Analytic Deviancy (SAMD) statistic was computed using SAS 8.2. Programming code for this analysis appears in Appendix O while the results are displayed in Table 22. In addition, scree plots were constructed to visually identify outliers and are presented in Appendix Q. Effect sizes with a SAMD statistic greater than 3.0 were considered extreme observations.

Table 22

Test for outliers among effect sizes for hypothesis two

Construct	Study	d	SAMD
Acute Stress	McNaughton-Cassill et al. (2002)	0.796	2.18
	Terzioglu (2001)	.5942	1.77
	Connolly et al. (1993)	.3783	1.11
	Emery et al. (2003)	.3182	0.80
	Emery et al. (2003)	.2582	0.56
Chronic Stress	Emery et al. (2003)	-.2818	1.11
	Emery et al. (2003)	.1854	0.85
Depression	Connolly et al. (1993)	1.1628	4.23
	Terzioglu (2001)	1.2932	4.14
	Emery et al. (2003)	.4564	1.17
	McNaughton-Cassill et al. (2002)	.0964	0.18
	Emery et al. (2003)	.2006	0.14

Based on this analysis, two studies were identified as outliers:

1. Connolly et al. (1993)

2. Terzioglu (2001)

These studies were examined for any differences in the populations or conditions that may account or explain the extreme observations. In the study conducted by Terzioglu (2001), the treatment group received support from a nurse practitioner that worked with all of the participants throughout the duration of the

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treatment. In addition, the nurse practitioner was present at the time of oocyte retrieval and embryo transfer. This was a distinct difference from the remainder of the studies who reported limited number of counseling sessions with the patients. However, there were no notable differences in the study conducted by Connolly et al. (1993) as compared to the remainder of the studies.

Next, a homogeneity test was conducted to determine whether the sample effect sizes for the 12 data points in the meta-analysis were homogenous. SAS 8.2 was used to perform the homogeneity test (see Appendix P). As shown in Table 23, the Q-statistic for measures of depression were significant at the .05 level, indicating that effect sizes are not homogeneous. Excluding the extreme observations as identified by the SAMD statistic, the Q-statistic was not significant at the .05 level for any of the measures, suggesting that the data are homogenous.

Table 23

Test of homogeneity of effect sizes for hypothesis two

Source	Including Outliers			Excluding Outliers		
	df	Q-Stat	p	df	Q-Stat	p
Acute Stress	4	2.47318	0.64944	4	2.47318	0.64944
Chronic Stress	1	1.74720	0.18623	1	1.74720	0.18623
Depression	4	16.8918	0.00203	2	0.95471	0.62042

To analyze the effects of psychoeducational interventions on the stress experienced by participants in an ART treatment program, a regression analysis was conducted (SAS code is presented in Appendix R). Two hypothesis tests

were conducted. First, the null hypothesis for the regression coefficient β_q for

any q = 0,1,2 is as follows:

$$H_0 : \beta_q = 0.$$

The regression coefficients represent the variable construct (acute stress

and chronic stress). Results including outliers and excluding outliers are

presented in Table 24. Results including study outliers show a moderate positive

relationship between psychoeducational interventions. However, neither the

estimates for acute stress or chronic stress was statistically significant. When

the study outliers were excluded from the analysis, results indicate that none of

the coefficients are statistically significant at the .05 level.

Table 24

Hierarchical random effects analysis for hypothesis two

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI		Estimate	p-value	95% CI	
			Lower	Upper			Lower	Upper
Intercept	0.6924	.03590	0.08591	1.29880	0.2681	0.1342	-0.15040	0.68660
Acute Stress	-0.2285	0.3483	-0.77810	0.32110	0.1688	0.3620	-0.28710	0.62470
Chronic Stress	-0.5885	0.1012	-1.33280	0.15580	-0.3157	0.1913	-0.87370	0.24220

Note. A total of 4 studies representing 12 effect sizes were included in the analysis including outliers.
A total of 4 studies representing 10 effect sizes were included in the analysis excluding outliers.

The null hypothesis for the random effects variance:

$$H_0 : \sigma^2_\theta = 0.$$

was tested. This hypothesis was tested by computing a weighted least squares

regression with weights equal to $w_i = \dfrac{1}{v_i}$. The weighted residual sum of squares

was compared with the critical values of chi-square distribution with $k - p - 1$

degrees of freedom. As shown in Table 25, the residual variance estimate is

significant at the .05 level for results including and excluding outliers.

Table 25

Hierarchical random effects variance analysis for hypothesis two

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI[a]		Estimate	p-value	95% CI[a]	
			Lower	Upper			Lower	Upper
Intercept	0.03762	0.3007	0.00569	0.11096	0			
Residual	1.87680	0.0349	0.80380	8.26460	0.73930	0.0307	0.32320	3.06240

[a]Due to different formulas used in the inferential statistics reported above, the 95% CI results may conflict with the significance test.
Note. A total of 4 studies representing 12 effect sizes were included in the analysis including outliers. A total of 4 studies representing 10 effect sizes were included in the analysis excluding outliers.

SAS code for computing the coefficients and conducting the analysis is listed in

Appendix S.

Since construct (acute stress and chronic stress) did not significantly

contribute to the model, a null model was constructed (see Appendix R). Results

of this analysis found that the intercept was not statistically significant when

either study outliers were included or excluded. These results indicate that while

the estimates demonstrate a small positive effect of psychoeducational

interventions on the stress experienced by women participating in an ART

treatment program when outliers are excluded, this effect is not statistically

significant (see Table 26). However, it is important to note that the number of

studies included in this analysis was small, limiting the power of this analysis.

Table 26

Hierarchical random effects null model analysis for hypothesis two

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI		Estimate	p-value	95% CI	
			Lower	Upper			Lower	Upper
Intercept	0.53420	0.0589	-0.03736	1.10570	0.30710	0.0527	-0.00670	0.62090

Note. A total of 4 studies representing 12 effect sizes were included in the analysis including outliers. A total of 4 studies representing 10 effect sizes were included in the analysis excluding outliers.

In addition, the analysis of the variance estimates including outliers as well as excluding outliers reveal statistically significant results for the residual estimates (1.9837 and 1.109, respectively) and are presented in Table 27.

Table 27

Hierarchical random effects null model variance analysis for hypothesis two

Parameter	Including Outliers				Excluding Outliers			
	Estimate	p-value	95% CI [a]		Estimate	p-value	95% CI [a]	
			Lower	Upper			Lower	Upper
Intercept	0.07452	0.2171	0.01625	22.75280	0.00584	0.4230	0.00051	1.02300
Residual	1.98370	0.0187	0.92790	6.81030	1.10900	0.0275	0.49280	4.38120

[a]Due to different formulas used in the inferential statistics reported above, the 95% CI results may conflict with the significance test.

Note. A total of 4 studies representing 12 effect sizes were included in the analysis including outliers.

A total of 4 studies representing 10 effect sizes were included in the analysis excluding outliers.

CHAPTER FIVE: CONCLUSIONS

Purpose of Research

The literature is replete with the psychological impacts of infertility, providing evidence that at least some women who confront infertility are at risk for heightened distress and depressive symptoms. Although research over the past several decades documents the prevalence of distress and depressive symptoms in infertile women, research findings provide conflicting evidence regarding the effects of stress and depression on ART treatment outcomes. Based on mounting evidence about the stress of infertility and infertility treatment, some investigators have suggested that infertility treatment programs should incorporate a psychological treatment component. As early as 1959, acute psychological supports for infertile couples as an adjunct to medical treatment can be found. Recently, national organizations such as Resolve, Inc. in the United States and the National Association for the Childless in the UK offering referral support groups and infertility counseling have been established (Anderson & Alesi, 1997). Although the debate regarding the impact of stress on ART treatment outcomes has yet to be resolved, it has been argued that biochemical treatment for infertility along with treatment for psychosocial stress could markedly improve overall reproduction outcomes (Wasser et al., 1999). These cultural trends along with the mounting empirical evidence have led many

reproductive endocrinologists to acknowledge the importance of psychoeducational interventions, regardless of their impact on ART treatment outcomes.

While several theoretical models postulate the effects of stress on ART treatment outcomes, a synthesis of the accumulated data incorporating a qualitative assessment of the methodology of reviewed studies and a quantitative method of combining and analyzing the data examining the effects of stress on ART treatment outcomes was nonexistent until the conduct of this study. Although practitioners and researchers have postulated that psychoeducational interventions may provide an important component to the treatment of infertility and may prove effective in preventing the anticipated increase in psychological distress as the duration of infertility increases, research on this topic is in its' infancy. Therefore, the purpose of this meta-analysis was two-fold. The first aim of this study was to investigate the impact of stress on the success of ART treatments through a review of the accumulated research. The second purpose of this study was to investigate the efficacy of psychoeducational interventions in mitigating the impact of stress experienced by women participating in an ART treatment program.

Overview of Method

Four primary processes were incorporated into this study:

1. The formulation of the problem,

2. The collection of data and relevant research studies,

3. The evaluation of the data, and

4. The analysis and interpretation of the results.

Based on the purposes identified for this synthesis, the two hypothesis were tested in this meta-analysis:

1. Increased levels of stress reduce the likelihood of ART treatment success, and

2. Psychoeducational interventions mitigate the effects of stress experienced by women participating in an ART treatment program.

Because it was expected that the studies to be included in the analysis would differ from one another in study characteristics and effect size parameter, both hypotheses were analyzed through a random effects model. Furthermore, a random effects model, asserting that the studies to be included in the analysis differ from the possible studies in the universe as a consequence of sampling procedures, addresses one common criticism of primary research investigating the relationship between stress and infertility treatment outcomes of homogeneous groups represented in the samples. The conceptualization of this study implies that the studies included in the analysis are different from one another in ways too complex to capture by the inclusion of simple study characteristics.

Studies included in this meta-analysis were located through an exhaustive comprehensive search of the English language literature from January 1985 through December 2003. Electronic searches were conducted through a variety of databases including MEDLINE/PubMed, ERIC, Psychinfo, and Dissertation Abstracts Online. Electronic branching from primary studies identified in this

search was also conducted to locate any additional studies similar in nature. Following the search of relevant electronic databases, manual scans of reference lists and other publications was conducted to identify any additional relevant studies. In addition, a search for registered clinical trials being conducted in the field of reproductive endocrinology was performed. Finally, researchers current and active in this field research were contacted in an effort to locate any additional studies, published as well as unpublished, left uncovered in the original search. Using this method, a total of 427 published research articles, one conference abstract, and three doctoral dissertations were located for hypothesis one. Of these articles, a total of 32 published studies, one conference abstract, and two doctoral dissertations were empirical investigations of the relationship between stress and ART treatment outcomes. For hypothesis two, the literature search revealed a total of 62 published studies and articles and one dissertation. Among these articles located, 21 published articles and one doctoral dissertation reported the results of empirical investigations of the relationship between psychoeducational interventions and stress.

Once all studies were located through the search of the literature, this researcher reviewed each article to ensure all studies meeting specified criteria for inclusion in the meta-analysis were identified. For each hypothesis, each study included in the meta-analysis met all of the following inclusion criteria:

1. For hypothesis one, the study must have involved situations where women were participating in an ART treatment program and the focus of the study was on the relationship between stress and ART treatment

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outcomes. For hypothesis two, the study must have involved women participating in a psychoeducational intervention program and an ART treatment program. The focus of the study was on the relationship between psychoeducational interventions and stress.

2. The study must have been conducted between January 1985 and December 2003 and prospective in design.

3. The study must report outcome measures of stress or anxiety and treatment outcomes. For hypothesis one, treatment outcome was defined achieving pregnancy or failure to achieve pregnancy. For hypothesis two, treatment outcome was defined as the post-treatment score of the stress measures.

4. Studies must be prospective in design.

The authors of studies meeting the above inclusion criteria but reporting insufficient data for effect size calculations were contacted in an effort to obtain all necessary data and information for inclusion in the meta-analysis. Studies in which all necessary information for effect size calculations was received were included in the analysis while studies for which there remained insufficient data for effect size calculations were excluded. Of the total 35 empirical investigations located through the literature review, 13 (37%) studies met the criteria for inclusion in the meta-analysis for hypothesis one. For hypothesis two, a total of 4 (18%) of the 22 studies located through the literature review met inclusion criteria.

Studies meeting the criteria for inclusion in the meta-analysis were subjected to a structured review of the quality of each study. This quality review applied the validity framework developed by Campbell and his associates, providing a matrix of design and study features (Wortman, 1994). A coding plan was developed to capture all relevant indicators including:

- Design

- Participants

- Controls/Implementation

- Protocol

- Outcomes

- Statistics,

producing a summary score to indicate the quality of each study. In addition to coding the quality of each study, characteristics of interest in each study were also captured. Information including publication characteristics, ecological characteristics, methodological characteristics, and results were recorded for each study. Both coding sheets, quality index and study characteristics coding forms, were subjected to a pilot test. Two professional evaluators current in the field of measurement and research were recruited to complete this pilot test. A total of six articles included in the meta-analysis for hypothesis one and two articles included in the meta-analysis for hypothesis two were randomly selected for the pilot test. Interrater agreement was assessed by comparing the values recorded by each coder for each of the variables of interest. Raters were in agreement if all coders recorded identical values. Results of the pilot test

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indicate a reasonably high interrater agreement rate. On the quality index form, the agreement rate was 92.65% while an agreement rate of 98.00% was found for the study characteristics form, resulting in an overall agreement rate of 94.09%.

Information collected on each study was then compiled and organized using a Microsoft Excel XP spreadsheet. Effect sizes were computed for each study. For hypothesis one, the effect size represented the magnitude of the influence of the influence of stress on ART treatment outcomes. For hypothesis two, the effect size represented the magnitude of the influence of psychoeducational interventions on an individual's level of stress while participating in an ART treatment program. The effect size metric computed for each analysis was Cohen's *d*. This effect size metric provided a common scale for comparison of study outcomes. Because of the complexity of the conceptualization of stress in infertility research, three separate constructs were represented in the analysis: acute stress, chronic stress, and depression. For studies reporting results from multiple measures of stress representing the same construct, Cohen's *d* effect sizes were calculated for each measure and then averaged to provide one statistic for each construct measured. In addition to multiple constructs, many studies reported results at multiple endpoints throughout the study. Effect sizes for studies providing measures at multiple points during the treatment program were computed separately and compared across studies using univariate analysis procedures. For studies failing to report

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relevant data and information to compute an effect size for nonsignificant findings, an effect size of 0 was assumed.

Statistical analysis of the resulting effect sizes from each study was conducted with SAS 8.2. Results culled from each study were combined by each endpoint and construct to provide an overall estimate of effect. The overall mean and variance of each effect size was determined, weighted by the sample size and study quality, estimating $\overline{T}_{.}$, the standardized mean difference. Next, a homogeneity test was conducted to determine whether the sample mean differences in each meta-analysis were homogenous. Once the overall mean and variance estimates across all studies was computed, the data was analyzed to identify extreme observations. To identify possible study outliers, the SAMD statistic was calculated. Finally, a fully hierarchical regression model using a mixed effects linear regression model was constructed for each hypothesis. For hypothesis one, this model was constructed utilizing the coefficients for each endpoint (baseline/pre-treatment, follicular phase, oocyte retrieval, embryo transfer, and follicular phase) and the coefficients computed for each construct (acute stress, chronic stress, and depression) as well as the corresponding null model. For each meta-analysis, two hypotheses were tested. First, the null hypothesis for the regression coefficient β_q for any q = 0, … , p as follows:

$$H_0 : \beta_q = 0.$$

In addition, the null hypothesis for the random effects variance was tested as follows:

$$H_0 : \sigma_\theta^2 = 0 \, .$$

Finally, a moderator analysis for the variables duration of infertility and country in which the study was performed for hypothesis one was conducted.

Summary of Findings

Effect sizes across studies investigating the relationship between stress and ART treatment outcomes were varied, ranging from –0.630 to 1.412, exemplifying the ongoing controversy on this topic. However, the overall mean effect size, 0.2748, demonstrates that there is a small relationship between stress and ART treatment outcomes indicating that stress does indeed impact treatment success negatively. While the only construct consistently reported for each endpoint (baseline/pre-treatment, follicular phase, oocyte retrieval, embryo transfer, and follicular phase) was acute stress, results support Menning's conceptualization of the crisis model applied to infertility. These findings demonstrate that infertility, to some extent, is a disruption in normal equilibrium.

It is important to note that five studies included in the meta-analysis for hypothesis one were identified as outliers. A sensitivity analysis showed that the inclusion of these studies in subsequent analyses did affect the results and implications. Therefore, a statistical analysis was conducted and reported for analyses including the outliers as well as excluding outliers. Statistical analysis investigating the relationship between stress and ART treatment outcomes revealed that neither the time (baseline/pre-treatment, follicular phase, oocyte retrieval, embryo transfer, and luteal phase) nor construct (acute or chronic

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stress) significantly contributed to the model regardless of whether the analysis included or excluded identified outliers. Therefore, a null model, pooling all effect sizes, was constructed. While the analysis including study outliers for the null model indicated that stress did not have a statistically significant effect on ART treatment outcomes, analysis excluding outliers revealed that stress does have a small effect on ART treatment outcomes, indicating that higher levels of stress have a negative effect on ART treatment outcomes. An analysis of the variance estimates for the null model excluding outliers reveals that both the intercept estimate (0.05271) and residual estimate (0.6279) are statistically significant indicating that the effect sizes pooled within each study varied greatly, while there is very little variability among the studies. A moderator analysis was also conducted for the variables duration of infertility and country in which the study was conducted. The results of this analysis demonstrated that, with study outliers excluded, neither the variable duration of infertility nor the variable country in which the study was conducted acted as a moderating variable.

The Q-statistic for results culled for hypothesis two revealed that there is a moderately positive effect ($d = 0.48052$) of psychoeducational interventions in mitigating the effects of stress for women participating in an ART treatment regime. The SAMD statistic identified two studies as extreme observations. Therefore, the HLM regression analyses including as well as excluding outliers were conducted and reported. Excluding outliers, the HLM regression analysis revealed that none of the coefficients computed were statistically significant. However, an analysis of the variance estimates revealed that the residual

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variance estimate (0.7393) was statistically significant. Based on these results, the null model, pooling effect sizes, was constructed. This analysis reveals that while psychoeducational interventions demonstrate a small positive effect on mitigating stress experienced by women participating in an ART treatment program, this coefficient was not statistically significant at the .05 level. However, the residual variance estimate (1.1090) was statistically significant, revealing a large amount of variability among the effect sizes pooled within each study.

Limitations of Study

One limitation to this study was the inability to include many of the primary studies that have been conducted to date due to insufficient amounts of data reported, specifically among the studies located for hypothesis one. This limitation manifested its' significance when conducting the HLM regression analysis. Ideally, this analysis would include the interaction effects of time (baseline-pre-treatment, follicular phase, oocyte retrieval, embryo transfer, and luteal phase) and construct (acute stress, chronic stress, and depression). However, due to the limitations in the available data, this analysis was not possible. In addition to the exclusion of studies due to insufficient data, one study included in the meta-analysis for hypothesis one reported an insufficient amount of data to compute effect sizes for statistically non-significant results. In these instances, the value of the effect size was 0, providing a conservative estimate of these results.

For the analysis investigating the efficacy of psychoeducational interventions on stress experienced by women participating an ART treatment program, the analysis as well as any generalizations that could be made was greatly limited because there was a total of only four studies meeting criteria for inclusion. Due to such a small number of studies included in the analysis, variables that may be operating as moderators could not be investigated in terms of their impact on findings. Because the investigation of psychoeducational interventions on the stress experienced by women participating in an ART treatment program is in its infancy, generalizations from this study should only be made to the four studies included in this analysis.

Another limitation to this study included the possibility of publication bias for studies investigating the effects of stress on ART treatment outcomes. As demonstrated in the funnel plot created, it appears that studies with smaller sample sizes reporting a negative effect, indicating that participants experiencing greater levels of stress were more likely to become pregnant following an ART treatment program, were not published. This could be a result of researchers, expecting stress to decrease the likelihood of ART treatment success, attributing unexpected results to sampling error or to small sample sizes and therefore, failing to submit this research for publication.

Implications

Based on the empirical evidence produced by this study, it appears that stress has a negative association with ART treatment outcomes. The value of the average effect size of 0.2012 indicates a small relationship. However, it is

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important to consider the 95% confidence interval that illustrates the possibility of this value to range between a very small relationship of 0.03007 and a moderate relationship of 0.37240. These results suggest that a purely biotechnological approach may not be successful in treating infertility for some women. In addition, in this analysis, it was found that the effects were consisitent across time and constructs measured. However, the residual variance was statistically significant, indicating that among the effect sizes pooled within studies, significant variability exists. These results suggest the need for continued research aimed at describing theoretical models explaining this relationship between stress and ART treatment outcomes. Specifically, sufficient amounts of information allowing a research synthesist to construct a regression model investigating the interaction effects between time (baseline/pre-treatment, follicular phase, oocyte retrieval, embryo transfer, and luteal phase) and construct (acute stress, chronic stress, and depression) would be valuable.

Although the results investigating the effects of psychoeducational interventions on the stress experienced by women participating in an ART treatement program were statistically insignificant, it is important to recognize the large amount of sampling error, as demonstrated by the 95% confidence interval ranging from −0.00670 to 0.62090. In addition, because the number of studies included in this analysis was very small, the power of the analysis was limited. Therefore, programs addressing the stress experienced by some women participating in an ART treatment program may not only be an ethical provision that reproduction endocrinologists provide to their patients, but may also be an

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additional variable to consider when the initial evaluation regarding the appropriateness of ART as a treatment option for a couple experiencing infertility is completed.

Implications for Further Research

Although this study has established that a statistically significant relationship exists between stress and ART treatment outcomes, many questions still exist. The variance estimates of the analysis indicate that while effect sizes did not differ greatly across studies, there is a large amount of variability among the effect sizes within each study. The differences among these studies as well as the impact of other possible moderating variables such as the level of education, the number of previous ART treatment attempts and etiology of infertility remain unknown. Therefore, scientists should continue research on this topic, incorporating and reporting information regarding possible moderating variables and investigating explanatory models of these findings. Furthermore, it is critical that all data gathered through these empirical investigations be reported and made available, allowing research synthesis studies to include all data accumulated. Finally, research synthesists conducting future analysis of the relationship between stress and ART treatment outcomes may consider disaggregating the data further by the construct measured. Specifically, while this study examined the effects for the following constructs:

- Acute Stress,
- Chronic Stress and
- Depression,

researchers should consider disaggregating the data further by physiological measures (such as heart rate, etc.) and psychometric measures (such as the State-Trait Anxiety Inventory, etc.) of the stress response.

Studies investigating the effects of psychoeducational interventions on the stress experienced by women participating in an ART treatment program continue to be important for the advancement of effective treatment programs. Furthermore, studies investigating the effects of a variety of psychoeducational interventions are needed. Studies investigating the effects of psychoeducational interventions should include, but are not limited to, the following widely accepted formats for treating psychological distress:

- Individual psychotherapy interventions,
- Cognitive behavioral approaches,
- Counseling programs (individual and group), and
- Patient education programs and support groups.

Studies implemented through a variety of designs such as pre-treatment counselling as well as interventions initiated before treatment begins and continuing through the conclusion of the ART treatment regime would provide additional information regarding educational formats most effective in mitigating stress. Information valuable to the interpretation of these findings includes the frequency of the intervention, the time length of each session, the duration of the program, and format. Finally, women participating in a psychoeducational intervention may be more proactive about treatment options as well as less secretive about their infertility, building more substantial social supports and

networks. Studies incorporating varying levels of social support or other variables, such as locus of control (external versus internal), which may confound results may help to identify any additional moderating variables. Finally, studies in this field of research should strive to triangulate methods, incorporating the valuable qualitative information published to date.

An implication for further research resulting from this study includes the investigation into a methodological issue. Specifically, the formulas used to calculate the confidence intervals in the Proc Mixed command in SAS. Conventional methods used for computing confidence intervals have been developed and are successfully used with univariate statistics. However, when applied to multivariate or mixed models, these conventional methods for computing the confidence interval do not appear to be very effective. Specifically, using the Proc Mixed command in SAS, the computations for confidence intervals for the variance components appear to only include the value of 0 if the variance estimate is 0 itself. Therefore, there would never be a nonzero variance component with a confidence interval including 0. Because the test of significance and the confidence intervals are computed differently, conflicting results may arise when the variance components are very small. As the use of mixed models and multivariate level statistics becomes more popular among researchers, applied researchers should address this interesting methodological issue, providing alternative methods for constructing the confidence intervals in these situations.

Closing Remarks

While to some, infertility represents a social state of childlessness, to many women and couples experiencing infertility, it can be a devastating experience, causing great levels of stress and turmoil. As the numbers of couples seeking treatment for infertility rises, the issues surrounding infertility represent a growing health problem. While technological advancements continue to provide couples experiencing infertility with additional options, physicians should begin to consider and provide couples assistance with the complex issues and emotional reactions to infertility. Research aimed at the advancement of understanding the complex relationship between stress and infertility, specifically ART treatment outcomes, should continue, providing physicians and couples with invaluable information regarding the physiological as well as the emotional experience of infertility and infertility treatment.

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APPENDICES

Appendix A: Electronic Databases Employed in Computerized Data Search

1. <u>MEDLINE/PubMed</u> which is the U.S. National Library of Medicine's premier bibliographic database that contains over 12 million references to journal articles in life sciences with a concentration on biomedicine.

2. <u>ClinicalTrials.gov</u>, which provides current information about clinical research studies for both federally and privately, funded trials.

3. <u>The Educational Resources Information Center (ERIC)</u> which includes <u>Current Index to Journals in Education (CIJE)</u>, indexing journal articles of interest to professionals in education, and <u>Resources in Education (RIE)</u> identifying unpublished educational reports and projects of significance.

4. <u>Psychinfo</u> which is the online version of <u>Psychological Abstracts</u>, providing information on published and unpublished work in psychology and related disciplines.

5. Dissertation Abstracts Online, which is the on-line version of Dissertation Abstracts International containing all of the dissertations, accepted from accredited American institutions in all subject areas.

Appendix B: Quality Review Form

Table 3

Evaluation of the quality of individual studies

Category		Questions	Response		
I. Design	a)	Is the design described?	Yes	No	N/A
	b)	Is the design appropriate to the study questions?	Yes	No	N/A
	c)	Is the design prospective?	Yes	No	N/A
	d)	Are there clear inclusion and exclusion criteria for participants?	Yes	No	N/A
	e)	Is there a description of each measure used and why it was chosen?	Yes	No	N/A
	f)	Are experimental methods, such as treatment schedules, clearly defined?	Yes	No	N/A
II. Participants	a)	Did the subjects meet the inclusion / exclusion criteria?	Yes	No	N/A
	b)	Are demographics for all subject groups reported including:			
		i. Age	Yes	No	N/A
		ii. Country or Race/Ethnicity	Yes	No	N/A
		iii. Economic Status	Yes	No	N/A
		iv. Employment Status	Yes	No	N/A
		v. Occupational Status	Yes	No	N/A
		vi. Education Level	Yes	No	N/A
		vii. Etiology of Infertility for infertile women	Yes	No	N/A
		viii. Classification of Infertility for infertile women	Yes	No	N/A
		ix. Duration of Infertility for infertile women	Yes	No	N/A
		x. Type of ART treatment received by infertile women	Yes	No	N/A
		xi. ART treatment History for infertile women	Yes	No	N/A

Table 3 (Continued)

IV. Controls / Implementation	a)	If there are parallel controls, are they comparable to the experimental group?	Yes	No	N/A
	b)	In a multi-group study, were the groups comparable at baseline for prognostic factors?	Yes	No	N/A
V. Protocol	a)	Were the treatment regimens followed?	Yes	No	N/A
	b)	Was the attrition rate low?	Yes	No	N/A
	c)	Was the implementation of the treatment / intervention protocol clearly described including:			
		i. Type of Treatment / Intervention	Yes	No	N/A
		ii. Duration of Intervention	Yes	No	N/A
		iii. Length of Time for each Intervention	Yes	No	N/A
		iv. Frequency of Intervention	Yes	No	N/A
VI. Outcomes	a)	Are the outcomes clearly defined, including methods of measurement?	Yes	No	N/A
	b)	Do the outcome measures answer the study questions?	Yes	No	N/A
VIII. Statistics	a)	Are the analytic methods clearly described	Yes	No	N/A
	b)	Are the analytic methods appropriate for the data and study design?	Yes	No	N/A
	c)	Are the summary statistics needed for the calculation of effect size in the paper or available from the investigator?	Yes	No	N/A
	d)	Are non-significant statistics reported?	Yes	No	N/A

Appendix C: Study Characteristics Important to Coding

I. Publication Characteristics

    A. Title

    B. Year of Study

    C. Authors

II. Ecological Characteristics

    A. Age

    B. Ethnicity

    C. Socio-Economic Status

    D. Etiology, Classification, and Duration of Infertility

    E. Type of ART Treatment and ART Treatment History

    F. Psychoeducational Intervention, Duration and Frequency of Intervention

III. Methodological Characteristics

    A. Sample Size

    B. Sampling Method

    D. Measure(s) of Stress or Anxiety

    E. Measure(s) of ART Success (pregnancy / live birth rate)

    F. Research Design

IV. Results

    A. Group Means and Standard Deviations

    B. Significance Level

    C. Other: F statistic, Chi-square, Correlation, etc.

Appendix D: Study Coding Sheet

Study Coding Form
Meta-Analysis Coding Part I: Increased levels of stress will reduce the likelihood of ART treatment success.

STUDY TITLE:

I. *Qualifying the study:*

For each study, answer the following questions as either "yes" or "no".

1. Does the study involve women participating in an ART treatment program?

2. Does the study focus on the relationship between stress and ART treatment outcomes?

3. Was the study conducted between January 1985 and December 2003?

4. Does the study employ a prospective design?

5. Does the study report outcome measures of stress or anxiety as well as ART treatment outcomes?

If the answer to each of the above questions is yes, the study qualifies for inclusion in the meta-analysis.

Study Coding Form
Meta-Analysis Coding Part II: Psychoeducational interventions provided to
patients receiving infertility treatment will mitigate the effects of stress during
Assisted Reproductive Technology (ART) treatment

STUDY TITLE:

I. *Qualifying the study:*

For each study, answer the following questions as either "yes" or "no".

1. Does the study involve women participating in a psychoeducational
    intervention program and an ART treatment program?

2.   Does the study focus on the relationship between the psychoeducational
    intervention and stress?

3. Was the study conducted between January 1985 and December 2003?

4. Does the study employ a prospective design?

5. Does the study report outcome measures of stress by category (treatment
    group versus control group if applicable)?

If the answer to each of the above questions is yes, the study qualifies for
inclusion in the meta-analysis.

Appendix D: (Continued)

II. Coding the study:

Please provide the following information about the study. If the requested
information is not available in the study documentation, leave it blank. Some
questions require you to choose from a set of options. Circle all that apply.

__A. Publication Characteristics__

    1. Title of the study:_____

    2. Year of Publication:_____

    3. Authors:_____

__B. Ecological Characteristics__

    1. Age of Female Participants: Mean:_____Range:_____

    2. Country:_____

    3. Race:

a. White	N:_____	%:_____
b. Black	N:_____	%:_____
c. Hispanic	N:_____	%:_____
d. Asian / Pacific Islander	N:_____	%:_____
e. American Indian	N:_____	%:_____
f. Other	N:_____	%:_____

Appendix D: (Continued)

4. Economic Status

    By Category:

        a. Low   N:_____   %:_____

        b. Low - Middle   N:_____   %:_____

        c. Middle   N:_____   %:_____

        d. Middle   N:_____   %:_____

        e. Upper - Middle   N:_____   %:_____

        f. High   N:_____   %:_____

    By Range:

        a. < 21,000   N:_____   %:_____

        b. $21,000 - $40,000   N:_____   %:_____

        c. $41,000 - $60,000   N:_____   %:_____

        d. > $60,000   N:_____   %:_____

5. Employment Status

        a. Yes   N:_____   %:_____

          i. Part-Time   N:_____   %:_____

          ii. Full-Time   N:_____   %:_____

        b. No   N:_____   %:_____

        c. Unknown   N:_____   %:_____

6. Occupational Status

        a. Labor   N:_____   %:_____

        b. Secretarial   N:_____   %:_____

        c. Professional   N:_____   %:_____

Appendix D: (Continued)

7. Yrs Education (Females): Mean:_____ Range:_____

    a. Elementary / Intermediate N:_____ %:_____

    b. Secondary N:_____ %:_____

    c. Secondary Graduate N:_____ %:_____

    d. Post-Secondary N:_____ %:_____

    e. Higher Education N:_____ %:_____
       Graduate

8. Etiology of Infertility

    a. Female Factor N:_____ %:_____

      i. Peritoneal Factors N:_____ %:_____

      ii. Endocrine Disorders N:_____ %:_____

      iii. Mechanical Factors N:_____ %:_____

      iv. Idiopathic N:_____ %:_____

    b. Male Factor N:_____ %:_____

    c. Combination N:_____ %:_____

9. Classification of Infertility

    a. Primary N:_____ %:_____

    b. Secondary N:_____ %:_____

10. Duration of Infertility: Mean:_____ Range:_____

    a. 1 – 3 year N:_____ %:_____

    b. 4 – 6 years N:_____ %:_____

    c. 7 – 9 years N:_____ %:_____

    d. > 9 years N:_____ %:_____

Appendix D: (Continued)

11. Type of ART Treatment (Please Choose)

    a. Gamete Intrafallopian Transfer (GIFT)

    b. Zygote Intrafallopian Transfer (ZIFT)

    c. In Vitro Fertilization (IVF)

    d. Intra-Cytoplasmic Sperm Injection (ICSI)

12. Previous ART Treatment Attempts: Mean:_____Range:_____

    Reported by Number:

a. 0	N:_____	%:_____
b. 1	N:_____	%:_____
c. 2	N:_____	%:_____
d. 3	N:_____	%:_____
e. 4 or >	N:_____	%:_____

    Reported by Ranges:

a. 0	N:_____	%:_____
b. 1 - 2	N:_____	%:_____
c. 2 - 3	N:_____	%:_____
d. 3 - 4	N:_____	%:_____
e. > 4	N:_____	%:_____

13. Psychoeducational Intervention (Please choose)

    a. Counseling

    b. Support Group

    c. Group Behavioral / Cognitive Behavioral Format

    d. Other:_____

Appendix D: (Continued)

14. Duration of Psychoeducational Intervention (Please choose)

      a. Daily for duration of ART treatment

      b. 1 – 3 sessions during ART treatment

      c. 6 weeks during ART treatment

      d. 8 weeks during ART treatment

      e. 10 weeks during ART treatment

      f. Other:_____

15. Length of Psychoeducational Intervention (Please choose)

      a. 1 hour

      b. 1.5 hours

      c. 2 hours

      d. Other:_____

16. Frequency of Psychoeducational Intervention (Please choose)

      a. Daily

      b. Weekly

      c. Bi-Weekly

      d. Other:_____

Appendix D: (Continued)

C. Methodological Characteristics

    1. Measure used for assessment

        a. Anxiety Measures

        b. Depression Measures

        c. Mood State Measures

        d. Infertility Stress Measures

        e. Physiological Stress Response Measures

    2. Time of Measure

        a. Anxiety Measures

        b. Depression Measures

        c. Mood State Measures

        d. Infertility Stress Measures

        e. Physiological Stress Response Measures

Appendix D: (Continued)

3. Sample Size of groups:

      Total N:_____

        a. 1   N:_____   %:_____

        b. 2   N:_____   %:_____

        c. 3   N:_____   %:_____

        d. 4   N:_____   %:_____

4. Sampling Method

        a. Random

        b. Convenience

5. Research Design

        a. Prospective

        b. Retrospective

D. Results

1. Significance levels for findings:

        a. Measure:_____

                Time:_____Results:_____

                Time:_____Results:_____

                Time:_____Results:_____

        b. Measure:_____

                Time:_____Results:_____

                Time:_____Results:_____

                Time:_____Results:_____

Appendix D: (Continued)

c. Measure:_____

       Time:_____Results:_____

       Time:_____Results:_____

       Time:_____Results:_____

       Time:_____Results:_____

d. Measure:_____

       Time:_____Results:_____

       Time:_____Results:_____

       Time:_____Results:_____

       Time:_____Results:_____

e. Measure:_____

       Time:_____Results:_____

       Time:_____Results:_____

       Time:_____Results:_____

       Time:_____Results:_____

f. Measure:_____

       Time:_____Results:_____

       Time:_____Results:_____

       Time:_____Results:_____

       Time:_____Results:_____

Appendix D: (Continued)

2. Other results, such as t-tests, F statistics, correlations, etc.

    a. Measure:_____

        Time:_____Results:_____

        Time:_____Results:_____

        Time:_____Results:_____

        Time:_____Results:_____

    b. Measure:_____

        Time:_____Results:_____

        Time:_____Results:_____

        Time:_____Results:_____

        Time:_____Results:_____

    c. Measure:_____

        Time:_____Results:_____

        Time:_____Results:_____

        Time:_____Results:_____

        Time:_____Results:_____

    d. Measure:_____

        Time:_____Results:_____

        Time:_____Results:_____

        Time:_____Results:_____

        Time:_____Results:_____

Appendix D: (Continued)

 e. Measure:_____

    Time:_____Results:_____

    Time:_____Results:_____

    Time:_____Results:_____

    Time:_____Results:_____

 f. Measure:_____

    Time:_____Results:_____

    Time:_____Results:_____

    Time:_____Results:_____

    Time:_____Results:_____

3. Means and Standard Deviations

Biologic Measure	Time:				Time:				Time:			
	Group:		Group:		Group:		Group:		Group:		Group:	
	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD
SBP												
DBP												
HR												
Cortisol												
Prolactin												
Other:												
Other:												
Other:												

Standard Measure	Sub-scale	Time:				Time:				Time:			
		Group:		*Group:*		*Group:*		*Group:*		*Group:*		*Group:*	
		$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD
BDI	PC												
	Vital												
	Total												
CPQ	I												
	II												
IQ													
MMQ													
PANAS													
POMS	1												
	2												
	3												
	4												
	5												
	6												
	Total												
STAI	State												
	Trait												
WOC	I												
	II												
	III												
	IV												
	V												
Other:													
Other:													

Appendix E: Coding Manual

I. Publication Characteristics

    A. Title – List the title of the Study

    B. Year of Publication – List the publication year

    C. Authors – List the author's last names

II. Ecological Characteristics

    A. Age – List the Mean age and range of ages for the females

    B. Country – List the country of where the study was performed

    C. Race – List the total number (N) and the percentage (%) for each category

    D. Economic Status – Record the total number (N) and the percentage (%) for either the category or by range

    E. Employment Status – Record the total number (N) and percentage (%) of the female participant's employment during the study. For those who were employed, record the total number (N) and percentage (%) for either part-time or full-time.

    F. Occupational Status – Record the total number (N) and percentage (%) for each type of occupation

    G. Yrs Education (Females) – Record the mean and range of the number of years of education for the female participants. If categorized according to level, record the total number (N) and percentage (%) for the female participants by level.

Appendix E: (Continued)

H. Etiology of Infertility – Record the reason for infertility. Female factors may be categorized by peritoneal (such as endometriosis or tubal factors), endocrine (such as anovulation), mechanical (such as cervical or uterine factors), or idiopathic (unexplained / unknown).

I. Classification of Infertility – Record the total number (N) and percentage (%) of women participating in the study identified as either primary or secondary infertility. (Women who report one or more parity / children are classified as secondary. Women who report zero parity / children and one or more spontaneous or selective abortion are classified as secondary. Women who report zero parity / children and zero abortions or previous pregnancies are classified as primary.)

J. Duration of Infertility – Refers to the length of time from original diagnosis or the length of time trying to conceive. Record the mean number of years and range of years. If categorized, record the total number (N) and percentage (%) for the appropriate range of years.

K. Type of ART Treatment – Circle all that apply for this study.

L. Previous ART Treatment Attempts – Record the mean number and range of the total number of ART treatments that women have undergone prior to the study. If the number is reported by number or ranges, record the total number (N) and percentage (%) for the appropriate category.

M. Psychoeducational Intervention – Circle all that apply that to this study. If the type is not listed as a choice, please fill in the name of the intervention in the "other" blank provided.

N. Duration of Psychoeducational Intervention – Circle how long the intervention is implemented during the ART treatment program. If the duration is not listed as a choice option, please fill in the duration of the intervention in the "other" blank provided.

O. Length of Psychoeducational Intervention – Circle how long (length in terms of time) each intervention session lasts. If the appropriate length of time is not provided as a choice option, please fill in the length of the intervention in the "other" blank provided.

P. Frequency of Intervention – Circle how often the intervention is implemented. If the appropriate frequency is not provided as a choice option, please fill in the length of the intervention in the "other" blank provided.

III. Methodological Characteristics

A. Measure(s) Used for assessment – Please list each measure used according to the construct it purports to represent.

B. Time of Measure – Using the following guide, record the time the assessment was administered according to the construct. If the time is not listed below, please record "9" and list the time of the measure:

1. Baseline (beginning of cycle) before administration of injections

2. Early follicular stage - after injections begin, but before oocyte retrieval

3. At the time of oocyte retrieval

4. At the time of embryo transfer

5. At the time of pregnancy test

6. 1 week following pregnancy test

7. 2 weeks following pregnancy test

8. 3 weeks following pregnancy test

9. Other

C. Sample Size – Record the total number included in the sample. Using the following guide, record the total number (N) and percentage (%) for each group of comparison:

1. Conceived or Treatment / Intervention group 1

2. Failed to Conceive or Treatment / Intervention group 2

3. Treatment / Intervention group 3

4. Control Group

D. Sampling Method – Choose whether participants were purely a convenience sample or whether participants were randomized into treatment groups

Appendix E: (Continued)

E. Research Design – Circle "prospective" if the study design included a

sample that had not yet participated in the ART treatment program at the

initiation of the study or "retrospective" if the participants completed the

measures of stress after the ART treatment program had already

concluded or as a follow-up.

IV. Results

A. Significance levels for findings – Record the measure used, the time of the

measure as described above (1 – 9), and the results (alpha level) of the

measure. If the study reports a measure only as "non-significant", record

the result as "NS".

B. Other results – This includes results from ANOVAs (F statistic), t-tests,

chi-square, correlations, etc. Record the measure used, the time of the

measure as described above (1 – 9), and all the results of the statistics

provided. For example, if an ANOVA was performed, in the space

provided for results, record the value of the F statistic, the degrees of

freedom, and the alpha level.

C. Means and Standard Deviations – Record information provided in the

appropriate space of the table. Standardized assessments are listed first,

followed by biological / physiological measures. For each result reported,

record the time of the measure as described above (1 – 9), the Group as

described above (1 – 4), the mean and standard deviation.

Appendix F: Empirical Studies Located for Meta-Analysis

Empirical Studies Meeting Inclusion Criteria for Hypothesis One

1. Ardenti, Rossella, Campari, Cinzia, Agazzi, Lorena, & La Sala, Giovanni Battista. (1999). Perceptive functioning of infertile women during IVF: Exploratory survey of an Italian sample. *Human Reproduction, 14(12), 3126-3132.*

2. Boivin, Jacky & Takefman, Janet E. (1995). Stress level across stages of in vitro fertilization in subsequently pregnant and nonpregnant women. *Fertility and Sterility*, 64(4), 802-810.

3. Csemiczky, György, Landgren, Britt-Marie, & Collins, Aila. (2000). The influence of stress and state anxiety on the outcome of IVF-treatment: psychological and endocrinological assessment of Swedish women entering IVF-treatment. *Acta Obstetricia et Gynecologica Scandinavica, 79, 113-118.*

4. Demyttenaere, Koen, Bonte, L., Gheldof, M., Vervaeke, M., Meuleman, C., Vanderschuerem, D., & D'Hooghe, T. (1998). Coping style and depression level influence outcome in in vitro fertilization. *Fertility and Sterility, 69(6), 1026-1033.*

5. *Demyttenaere, Koen, Nijs, Piet, Evers-Kiebooms, Gerry, & Koninckx, Philippe. (1992).* Coping and the ineffectiveness of coping influence the outcome of in vitro fertilization through stress responses. *Psychoneuroendocrinology, 17(6), 655-665.*

6. Facchinetti, Fabio, Volpe, Annibale, Matteo, Maria Lucia, Genazzani, Andrea R., & Artini, G. Paolo. (1997). An increased vulnerability to stress is associated with a poor outcome of in vitro fertilization-embryo transfer treatment. *Fertility and Sterility, 67(2), 309-314.*

7. Gallinelli, A., Roncaglia, R., Matteo, M. L., Ciaccio, I., Volpe, A., & Facchinetti, F. (2001). Immunological changes and stress are associated with different implantation rates in patients undergoing in vitro fertilization-embryo transfer. *Fertility and Sterility*, 76(1), 85-91.

8. Kee, Baik Seok, Jung, Byeong Jun, & Lee, Sang Hoon. (2000). A study on psychological strain in IVF patients. *Journal of Assisted Reproduction and Genetics, 17(8), 445-448.*

9. Merari, Dalia, Feldberg, Dov, Elizur, Avner, Goldman, Jacob, & Modan, Baruch. (1992). Psychological and hormonal changes in the course of in vitro fertilization. *Journal of Assisted Reproduction and Genetics, 9(2), 161-169.*

10. Merari, D., Feldberg, D., Shitrit, A., Elizur, A., & Modan, B. (1996). Psychosocial characteristics of women undergoing in vitro fertilization: a study of treatment outcome. *Israel Journal of Obstetrics and Gynecology, 7(2), 65-72.*

11. Sanders, K.A. & Bruce, N.W. (1999). Psychological stress and treatment outcomes following ART. *Human Reproduction, 14(6), 1656-1662.*

12. Thiering, P., Beaurepaire, J., Jones, M., Saunders, D., & Tennant, C. (1993). Mood state as a predictor of treatment outcomes after in vitro fertilization / embryo transfer technology (IVF/ET). *Journal of Psychosomatic Research, 37(5), 481-491.*

13. Verhaak, Christianne M., Smeenk, Jesper M.J., Eugster, Antje, van Minnen, Agnes, Kremer, Jan A.M., & Kraaimaat, Floris W. (2001). Stress and marital satisfaction among women before and after their first cycle of in vitro fertilization and intracytoplasmic sperm injection. *Fertility and Sterility, 76(3), 525-531.*

Empirical Studies Excluded from Meta-Analysis for Hypothesis One

Sample includes women not participating in an ART treatment program

1. Kemeter, Peter. (1988). Studies on psychosomatic implications of infertility – effects of emotional stress on fertilization and implantation in in-vitro fertilization. *Human Reproduction, 3(3), 341-352.*

2. Sanders, K.A. & Bruce, N.W. (1997). A prospective study of psychosocial stress and fertility in women. *Human Reproduction, 12(10), 2324-2329.*

3. Vartianinen, Heikki. (1990). Effects of psychosocial factors, especially work-related stress, on fertility and pregnancy: A prospective study from the stage of planning to become pregnant. (Doctoral dissertation, Kuopio University, 1989). *Acta Obstet. Gynecol. Scand., 69, 677-678.*

Focus is not on the relationship between stress and ART treatment outcome

4. Andersen, C. Yding, Westergaard, L.G., Teisner, B., Byskov, A.G., Ziebe, S., Helledie, L., Petersen, K., & Westergaard, J.G. (1992). Changes induced in serum protein profiles by ovarian stimulation during in-vitro fertilization-embryo transfer treatment: a comparison between conception and non-conception cycles. *Human Reproduction, 7(5), 585-591.*

5. Boivin, Jacky & Takefman, Janet E. (1996). Impact of the in-vitro fertilization process on emotional, physical and relational variables. *Human Reproduction, 11(4), 903-907.*

6. Demyttenaere, Koen, Nijs, Piet, Evers-Kiebooms, Gerry, & Koninckx Phillippe R. (1991). Coping, ineffectiveness of coping and psychoendocrinological stress responses during in-vitro fertilization. *Psychosomatic Research, 35(2/3), 231-243.*

7. Kee, B.S., Jung, B.T., & Lee, S.H. (2000). A study on psychological strain in IVF patients. *Journal of Assisted Reproduction and Genetics, 17(8), 445-448.*

8. Kowalcek, I., Kasimzade, T., & Huber G. (2003). Expectations for success in fertility treatment involving assisted reproduction. *Arch Gynecol Obstet., 268(2), 78-81.*

9. Milad, Magdy P., Klock, Susan C., Moses, Scott, & Chatterton, Robert. (1998). Stress and anxiety do not result in pregnancy wastage. *Human Reproduction, 13(8), 2296-2300.*

10. Phromyothi, V. & Virutamasen, P. (2003). The determinant factors and the anxiety level of infertile couples during the treatment of in vitro fertilization and embryo transfer at Chulalongkorn Hospital. *Journal of Med. Assoc. Thai., 86(5), 425-429.*

11. Salvatore, Paola, Gariboldi, Simonetta, Offidani, Ada, Coppola, Francesco, Amore, Mario, & Maggini, Carlo. (2001). Psychopathology, personality, and marital relationship in patients undergoing in vitro fertilization procedures. *Fertility and Sterility, 75(6), 1119-1125.*

12. Sharma, Vinay, Allgar, Victoria, & Rajkhowa, M. (2002). Factors influencing the cumulative conception rate and discontinuation of in vitro fertilization treatment for infertility. *Fertility and Sterility, 78(1), 40-46.*

13. Stoléru, S., Cornet, D., Vaugeois, P., Fermanian, J., Magnin, F., Zerah, S., & Spira, A. (1997). The influence of psychological factors on the outcome of the fertilization step of in vitro fertilization. *Journal of Psychosomatic Obstet. And Gynecol., 18, 189-202.*

14. Young, P., Martin, C., & Thong, J. (2000). A comparison of psychological functioning in women at different stages of in vitro fertilization treatment using the mean affect adjective check list. *Journal of Assisted Reproduction and Genetics, 17(10), 553-556.*

Retrospective design

15. Beutel, M, Kupfer, J, Kirchmeyer, P., Kehde, S., Köhn, F.M., Schroeder-Printzen, I., Gips, H., Herrero, H.J.G., & Weidner, W. (1999). Treatment-related stresses and depression in couples undergoing assisted reproductive treatment by IVF or ICSI. *Andrologia, 31, 27-35.*

Appendix F: (Continued)

Insufficient data reported

16. Chreac'h-Le Mer, M.N., Stoleru, S.G., Cornet, D., Zerah, S., Fermanian, J., Bimbard, S., Spira, A. (1999*). Women's anxiety is a predictor of the implantation step of in vitro fertilization.* Paper presented at the American Psychosomatic Society 57th Annual Scientific Meeting, Vancouver, B.C., Canada.
17. Harlow, C.R., Fahy, U.M., Talbot, W.M., Wardle, P.G., & Hull, M.G.R. (1996). Stress and stress-related hormones during in-vitro fertilization treatment. *Human Reproduction, 11(2), 274-279.*
18. Klonoff-Cohen, Hillary, Chu, Elaine, Natarajan, Loki, & Sieber, William. (2001). A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. *Fertility and Sterility, 76(4), 675-687.*
19. Lovely, Laurie P., Meyer, William R., Ekstrom, David, & Golden, Robert N. (2003). *Southern Medical Journal, 96(i6), 548-552.*
20. Slade, P., Emery, J., & Lieberman, B.A. (1997). A prospective, longitudinal study of emotions and relationships in in-vitro fertilization treatment. *Human Reproduction, 12(1), 183-190.*
21. Smeenk, J.M.J., Verhaak, C.M., Eugster, A., van Minnen, A., Zielhuis, G.A., & Braat, D.D.M. (2001). The effect of anxiety and depression on the outcome of in-vitro fertilization. *Human Reproduction, 16(7), 1420-1423.*

Paper unobtainable

22. Emery, Josephine Angela. (1993). Psychological aspects of IVF: a prospective study. Doctoral dissertation, University of Manchester, United Kingdom.

Empirical Studies Meeting Inclusion Criteria for Hypothesis Two

1. Connolloy, Kevin J., Edelmann, Robert J., Bartlett, Helen, Cooke, Ian D., Lenton, Elizabeth, & Pike, Sheila. (1993). An evaluation of counselling for couples undergoing treatment for in-vitro fertilization. *Human Reproduction, 8(8), 1332-1338.*
2. Emery, M., Béran, M.D., Darwiche, J., Oppizzi, L., Joris, V., Capel, R., Guex, P., & Germond, M. (2003). Results from a prospective, randomized, controlled study evaluating the acceptability and effects of routine pre-IVF counselling. *Human Reproduction, 18(12), 2647-2653.*
3. McNaughton-Cassill, Mary Ellen, Bostwick, J. Michael, Arthur, Nancy J., Robinson, Randal D., & Neal, Gregory S. (2002). Efficacy of brief couples support groups developed to manage the stress of in vitro fertilization treatment. *Mayo Clin Proc., 77, 1060-1066.*

4. Terzioglu, F. (2001). Investigation into effectiveness of counseling on assisted reproductive techniques in Turkey. *Journal of Psychosomatic Obstetrics and Gynecology, 22, 133-141.*

Empirical Studies Excluded from Meta-Analysis for Hypothesis Two

Sample includes women not participating in an ART treatment program

1. Domar, Alice D., Zuttermeister, Patricia C., Seibel, Machelle, & Benson, Herbert. (1992). Psychological improvement in infertile women after behavioral treatment: a replication. *Fertility and Sterility, 58(1), 144-147.*
2. Domar, Alice D., Seibel, Machelle M., & Benson, Herbert. (1990). The Mind/Body Program for infertility: a new behavioral treatment approach for women with infertility. *Fertility and Sterility, 53(2), 2469-249.*
3. Domar, Alice D., Slawsby, Ellen, Kessel, Bruce, Clapp, Diane, Oray, John, & Freizinger, Melissa. (2000). The impact of group psychological interventions on distress in infertile women. *Health Psychology, 19(6), 568-575.*
4. Domar, Alice D., Clapp, Diane, Slawsby, Ellen A., Dusek, Jeffery, Kessel, Bruce, & Freizinger, Melissa. (2000). The impact of group psychological interventions on pregnancy rates in infertile women. *Fertility and Sterility, 73(4), 805-811.*
5. Hsu, Y.L. & Kuo, B.J. (2002). Evaluations of emotional reactions and coping behaviors as well as correlated factors for infertile couples receiving assisted reproductive technologies. *Journal of Nursing Research, 10(4), 291-302.*
6. Liswood, Margaret Peggi. (1993). Treating the crisis of infertility: a cognitive-behavioral approach. Doctoral dissertation, University of Toronto, Canada.
7. Lukse, M.P. (1985). The effect of group counseling on the frequency of grief reported by infertile couples. *Journal of Obstetrics and Gynecology Neonatal Nursing, 14(6 Suppl), 67s-70s.*
8. McQueeney, Debra A., Stanton, Annette L., & Sigmon, Sandra. (1997). Efficacy of emotion-focused and problem-focused group therapies for women with fertility problems. *Journal of Behavioral Medicine, 20(4), 313-331.*
9. O'Moore, A.M., O'Moore, R.R., Harrison, R.F., Murphy, G., & Carruthers, M.E. (1983). Psychosomatic aspects in idiopathic infertility: effects of treatment with autogenic training. *Journal of Psychosomatic Research, 27(2), 145-151.*
10. Sarrel, Philip M. & DeCherney, Alan H. (1985). Psychotherapeutic intervention for treatment of couples with secondary infertility. *Fertility and Sterility, 43(6), 897-900.*

Appendix F: (Continued)

11. Stewart, Donna E., Boydell, Katherine M., McCarthy, Karolina, Swerdlyk, Susan, Redmond, Carol, & Cohrs, Wilma. (1992). A prospective study of the effectiveness of brief professionally-led support groups for infertility patients. *International Journal of Psychiatry in Medicine, 22(2), 173-182.*
12. Tuschen-Caffier, Bruna, Florin, Irmela, Krause, Walter, & Pook, Martin. (1999). Cognitive-behavioral therapy for idiopathic infertile couples. *Psychotherapy and Psychosomatics, 68, 15-21.*

Sample includes only men

13. Lottman, P.E., Hendriks, J.C., Vruggink, P.A., & Meuleman, E.J. (1998). The impact of marital satisfaction and psychological counselling on the outcome of ICI-treatment in men with ED. *International Journal of Impotence Research, 10(2), 83-87.*

Focus of the outcome measure(s) is not stress

14. Bartlam, Bernadette & McLeod, John. (2000). Infertility counselling: the ISSUE experience of setting up a telephone counselling service. *Patient Education and Counseling, 41, 313-321.*
15. Freeman, E.W., Boxer, A.S., Rickels, K., Tureck, T., & Mastroianni, L. Jr. (1985). Psychological evaluation and support in a program of in vitro fertilization and embryo transfer. *Fertility and Sterility, 43(1), 48-53.*
16. McNaughton-Cassill, Mary Ellen, Bostwick, Michael, Vanscoy, Sara E., Arthur, Nancy J., Hickman, Timothy N., Robinson, Randal D., & Neal, Greg S. (2000). Development of brief stress management support groups for couples undergoing in vitro fertilization treatment. *Fertility and Sterility, 74(1), 87-93.*
17. Pengelly, Paul, Inglis, Margaret, & Cudmore, Lynne. (1995). Infertility: Couples' experiences and the use of counselling in treatment centers. *Pyschodynamic Counselling, 1, 507-524.* Wischmann, T. Stammer, H., Scherg, H., Gerhard, I., & Verres, R. (2001). Psychosocial characteristics of infertile couples: a study by the "Heidelberg Fertility Consultation Service'. *Human Reproduction, 16(8), 1753-1761.*

Retrospective design

18. Weaver, Susan M., Clifford, Ellen, Hay, Douglas, & Robinson, John. (1997). Psychosocial adjustment to unsuccessful IVF and GIFT treatment. *Patient Education and Counseling, 31, 7-18.*

Appendix G: Conceptual Definitions of Constructs

Acute stress, defined as the momentary state experienced during the ART

treatment program, was represented using the following psychological measures:

1. Stait-Trait Anxiety Inventory (STAI) – state anxiety subtest,

2. Infertility Questionnaire,

3. Daily Infertility Records, and

4. POMS – tension / anxiety subtest.

The physiological measures of acute stress included:

1. Cortisol,

2. Prolactin,

3. Systolic Blood Pressure,

4. Diastolic Blood Pressure,

5. Heart Rate,

6. 6-SM,

7. FSH, and

8. Estradiol.

Chronic Stress is conceptualized in this study as anxiety or stress persisting over

a long duration of time. The following were included in the analysis as measures

of chronic stress:

1. STAI – trait anxiety subtest

Depression is conceptualized in this study as negative emotion of extreme

sadness.

Appendix G: (Continued)

The following were included in the analysis as measures of depression:

1. Becks Depression Inventory,

2. Center for Epidemiology Studies Depression Scale (CES-d),

3. Zung Depression Inventory,

4. DACL, and

5. POMS – depression / dejection subtest.

Appendix H: SAS Code for Combining Effect Sizes

```sas
TITLE 'COMBINING STANDARDIZED MEAN DIFFERENCES BY STRESS MEASURES AND
TIME';
DATA ORIG;
 INPUT ID 1-2 CONSTRUCT 4 TIME 6 AGE 8 COUNTRY 10 ETIOLOGY 12 DURATION
14 D 16-20 .3 N1 22-24 N2 26-28 QI 30-32 .2;
 T1 = 0;
 T2 = 0;
 T3 = 0;
 T4 = 0;
 T5 = 0;
 C1 = 0;
 C2 = 0;
 C3 = 0;
 ARRAY CON CONSTRUCT;
 ARRAY TIM TIME;
 DO OVER TIM;
  IF TIME = 1 THEN T1 = 1;
  IF TIME = 2 THEN T2 = 1;
  IF TIME = 3 THEN T3 = 1;
  IF TIME = 4 THEN T4 = 1;
  IF TIME = 5 THEN T5 = 1;
 END;
 DO OVER CON;
  IF CONSTRUCT = 1 THEN C1 = 1;
  IF CONSTRUCT = 2 THEN C2 = 1;
  IF CONSTRUCT = 3 THEN C3 = 1;
 END;
 T1C1 = T1*C1;
 T1C2 = T1*C2;
 T1C3 = T1*C3;
 T2C1 = T2*C1;
 T2C2 = T2*C2;
 T2C3 = T2*C3;
 T3C1 = T3*C1;
 T3C2 = T3*C2;
 T3C3 = T3*C3;
 T4C1 = T4*C1;
 T4C2 = T4*C2;
 T4C3 = T4*C3;
 T5C1 = T5*C1;
 T5C2 = T5*C2;
 T5C3 = T5*C3;
 *    +--------------------------------+
          COMPUTE CI FOR EACH STUDY
         +--------------------------------+;
V=((N1+N2)/(N1*n2))+((D**2)/(2*(N1+N2)));
LOWER = D - (1.96*SQRT(V));
UPPER = D + (1.96*SQRT(V));
 *    +---------------------------------------------------+
          WEIGHT STUDIES BY QUALITY INDEX & SAMPLE SIZE
         +---------------------------------------------------+;
```

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Appendix H: (Continued)

```
W = 1/V;
QISQ = QI**2;
QIW = QI*W;
QISQW = QISQ*W;
QIWD = QI*W*D;
DSQ = D**2;
WDSQ = W*DSQ;
WD = W*D;
WSQ = W**2;
N = N1 + N2;
CARDS;
01 1 3 0 3 1 0 0.459 011 029 .85
01 2 3 0 3 1 0 0.080 011 029 .85
03 1 1 2 3 0 1 -.071 017 023 .79
03 1 2 2 3 0 1 0.573 017 023 .79
03 1 3 2 3 0 1 0.806 017 023 .79
03 1 4 2 3 0 1 0.643 017 023 .79
03 1 5 2 3 0 1 0.866 017 023 .79
03 2 1 2 3 0 1 0.190 017 023 .79
06 1 1 1 2 0 2 1.412 047 091 .87
06 2 1 1 2 0 2 1.787 047 091 .87
06 3 1 1 2 0 2 0.949 047 091 .87
08 1 1 2 1 1 0 -.630 082 230 .92
08 2 1 2 1 1 0 -.061 082 230 .92
08 3 1 2 1 1 0 -.117 082 230 .92
09 1 1 2 3 1 1 0.199 039 088 .81
09 3 1 2 3 1 1 0.326 039 088 .81
10 1 3 2 3 1 2 -.616 038 162 .98
10 2 3 2 3 1 2 0.034 038 162 .98
11 1 1 1 1 1 0 0.498 032 024 .77
11 2 1 1 1 1 0 0.579 032 024 .77
12 1 1 2 3 2 0 0.865 009 013 .81
12 1 2 2 3 2 0 0.598 009 013 .81
12 1 5 2 3 2 0 1.528 009 013 .81
13 1 1 2 3 1 2 0.241 016 033 .88
13 1 3 2 3 1 2 0.437 016 033 .88
13 2 1 2 3 1 2 0.629 016 033 .88
14 1 2 1 3 1 2 0.473 010 030 .82
14 1 3 1 3 1 2 0.190 010 030 .82
14 1 4 1 3 1 2 0.000 010 030 .82
14 3 2 1 3 1 2 2.723 010 030 .82
20 1 2 0 2 1 0 -.212 023 090 .93
20 1 3 0 2 1 0 -.177 023 090 .93
20 1 4 0 2 1 0 0.065 023 090 .93
20 1 5 0 2 1 0 0.107 023 090 .93
20 2 1 0 2 1 0 0.048 023 090 .93
20 3 2 0 2 1 0 -.328 023 090 .93
20 3 3 0 2 1 0 -.306 023 090 .93
20 3 4 0 2 1 0 0.067 023 090 .93
20 3 5 0 2 1 0 -.007 023 090 .93
25 3 1 1 3 1 1 0.041 023 075 .91
28 1 1 2 2 1 3 0.024 023 090 .87
```

```
28 2 1 2 2 1 3 0.050 023 090 .87
28 3 1 2 2 1 3 -.332 023 090 .87
;
DATA FIRST;
 SET ORIG;
 IF T1C1 = 1;
PROC PRINT DATA = FIRST;
 TITLE 'SUMMARY STATISTICS FOR D';
 VAR ID D V N TIME CONSTRUCT LOWER UPPER QI W QISQW QIW QIWD WDSQ WD;
PROC MEANS SUM N DATA = FIRST;
 VAR N W WSQ WDSQ WD;
*      +------------------------------------------------+
          WRITE OUT SUMMARY STATISTICS FOR VARIANCES
       +------------------------------------------------+;
OUTPUT OUT = COMBINE
SUM = Total_N SW SWSQ SWDSQ SWD
MEAN = MNN
N = N1;
PROC PRINT;
 VAR SW SWSQ SWDSQ SWD MNN N1;
DATA COMBINE;
 SET COMBINE;
*      +------------------------------------------------+
          COMPUTE UNCONDITIONAL VARIANCE COMPONENT
       +------------------------------------------------+;
C = (SW -((SWSQ/SW)));
Q = SWDSQ - ((SWD**2)/SW);
Prob_Q = 1 - probchi(Q, N1 - 1);
DF = N1 -1;
BTWNV = (Q - (N1 - 1))/C;
EQ = C*BTWNV + (N1 -1);
PROC PRINT;
 VAR C Q DF PROB_Q BTWNV EQ;
*      +------------------------------------------------+
            COMPUTE TOTAL WEIGHTED VARIANCE
       +------------------------------------------------+;
DATA TWO;
 IF _N_ = 1 THEN SET COMBINE;
 SET FIRST;
WW = 1/(BTWNV + V);
WV1 = QISQ*WW;
WV2 = QI*WW;
WV2B = WV2**2;
IWV = WV1 / WV2B;
WQIWD = QI*WW*D;
PROC PRINT;
 TITLE 'SUMMARY STATISTICS FOR WEIGHTED D UNDER RANDOM EFFECTS MODEL';
 VAR ID D V LOWER UPPER IWV QI W WW WV1 WV2 WV2B WQIWD C Q BTWNV EQ;
 PROC MEANS SUM N;
  VAR N WW WV1 WV2 WQIWD;
```

Appendix H: (Continued)

```
*      +-------------------------------------------------+
          WRITE OUT SUMMARY STATISTICS TO COMBINE
       +-------------------------------------------------+;
OUTPUT OUT = RESULTS
SUM = Total_N SWW SWV1 SWV2 SWQIWD
MEAN = MNN
N = N1 N2 N3;
DATA REFINAL;
 SET RESULTS;
DPLUS = SWQIWD/SWV2;
WWV = SWV1/(SWV2**2);
VERROR = ((MNN-1)/(MNN-3))*(4/MNN)*(1+((DPLUS**2)/8));
UNBIASV = WWV - VERROR;
IF UNBIASV LT 0 THEN UNBIASV = 0;
A = 1+(0.75/(MNN-3));
SE = SQRT(WWV);
DPLUSC = DPLUS/A;
SEC = SE/A;
CLL = DPLUSC - (1.96*SEC);
CUL = DPLUSC + (1.96*SEC);
PROC PRINT;
 VAR SWV1 SWV2 WWV VERROR UNBIASV MNN A SE DPLUS DPLUSC SEC;
PROC PRINT;
 TITLE 'RANDOM EFFECTS WEIGHTED AVERAGE D AND VARIANCE';
 VAR DPLUSC SEC CLL CUL;
RUN
;
```

Appendix I: SAS Code for Calculating SAMD Statistic for Hypothesis One

```
TITLE 'COMBINING STANDARDIZED MEAN DIFFERENCES BY STRESS MEASURES AND
TIME';
DATA ONE;
INPUT SID 1-2 CONSTRUCT 4 TIME 6 AGE 8 COUNTRY 10 ETIOLOGY 12 DURATION
14 D 16-20 .3 N1 22-24 N2 26-28 QI 30-32 .2;
V = ((N1+N2)/(N1*N2)+((D**2)/(2*N1+N2)));
W = 1/V;
N = N1 + N2;
DN = D*W;
CARDS;
01 1 3 0 3 1 0 0.459 011 029 .85
01 2 3 0 3 1 0 0.080 011 029 .85
03 1 1 2 3 0 1 -.071 017 023 .79
03 1 2 2 3 0 1 0.573 017 023 .79
03 1 3 2 3 0 1 0.806 017 023 .79
03 1 4 2 3 0 1 0.643 017 023 .79
03 1 5 2 3 0 1 0.866 017 023 .79
03 2 1 2 3 0 1 0.190 017 023 .79
06 1 1 1 2 0 2 1.412 047 091 .87
06 2 1 1 2 0 2 1.787 047 091 .87
06 3 1 1 2 0 2 0.949 047 091 .87
08 1 1 2 1 1 0 -.630 082 230 .92
08 2 1 2 1 1 0 -.061 082 230 .92
08 3 1 2 1 1 0 -.117 082 230 .92
09 1 1 2 3 1 1 0.199 039 088 .81
09 3 1 2 3 1 1 0.326 039 088 .81
10 1 3 2 3 1 2 -.616 038 162 .98
10 2 3 2 3 1 2 0.034 038 162 .98
11 1 1 1 1 1 0 0.498 032 024 .77
11 2 1 1 1 1 0 0.579 032 024 .77
12 1 1 2 3 2 0 0.865 009 013 .81
12 1 2 2 3 2 0 0.598 009 013 .81
12 1 5 2 3 2 0 1.528 009 013 .81
13 1 1 2 3 1 2 0.241 016 033 .88
13 1 3 2 3 1 2 0.437 016 033 .88
13 2 1 2 3 1 2 0.629 016 033 .88
14 1 2 1 3 1 2 0.473 010 030 .82
14 1 3 1 3 1 2 0.190 010 030 .82
14 1 4 1 3 1 2 0.000 010 030 .82
14 3 2 1 3 1 2 2.723 010 030 .82
20 1 2 0 2 1 0 -.212 023 090 .93
20 1 3 0 2 1 0 -.177 023 090 .93
20 1 4 0 2 1 0 0.065 023 090 .93
20 1 5 0 2 1 0 0.107 023 090 .93
20 2 1 0 2 1 0 0.048 023 090 .93
20 3 2 0 2 1 0 -.328 023 090 .93
20 3 3 0 2 1 0 -.306 023 090 .93
20 3 4 0 2 1 0 0.067 023 090 .93
20 3 5 0 2 1 0 -.007 023 090 .93
25 3 1 1 3 1 1 0.041 023 075 .91
28 1 1 2 2 1 3 0.024 023 090 .87
```

Appendix I: (Continued)

```
28 2 1 2 2 1 3 0.050 023 090 .87
28 3 1 2 2 1 3 -.332 023 090 .87
;
PROC SORT;
 BY TIME CONSTRUCT;
DATA TC;
 SET ONE;
 IF TIME EQ 1 AND CONSTRUCT EQ 1;
PROC MEANS MEAN MAXDEC = 2;
 VAR D;
PROC MEANS SUM MAXDEC = 2;
 VAR DN;
PROC MEANS MEAN SUM N MAXDEC = 2;
 VAR N;
* +--------------------------------------------+
    USING THE RESULTS FROM ABOVE OUTPUT, INPUT THE
    DATA FOR COMPUTATIONS TO FOLLOW
  +--------------------------------------------+;
DATA TWO;
 SET TC;
MEAN_D = .32;
TOTAL_D = 15.22;
MEAN_N = 107.13;
TOTAL_N = 857;
K = 8;
* +--------------------------------------------+
    COMPUTATIONS EXCLUDING INDIVIDUAL STUDIES
  +--------------------------------------------+;
TOTAL_NW = TOTAL_N - N;
MEAN_DW = (TOTAL_D - DN)/TOTAL_NW;
VAR_I = (4*(N-1)*(1+((MEAN_DW**2)/8)))/(N*(N-3));
VAR_D = (4*(MEAN_N-1)*(1+((MEAN_DW**2)/8)))/(MEAN_N*(MEAN_N-3)*K);
SAMD_I = (D-MEAN_DW)/(SQRT(VAR_I+VAR_D));
SAMD = ABS(SAMD_I);
SAMDR = ROUND (SAMD,.01);
* +--------------------------------------------+
    RANK ORDERS THE SAMD FOR EACH STUDY
  +--------------------------------------------+;
PROC RANK DESCENDING OUT = TEMP;
 VAR SAMDR;
 RANKS RANK_ID;
PROC SORT;
 BY RANK_ID;
DATA THREE;
 SET TEMP;
FILE OUTPUT;
 PUT RANK_ID SAMDR;
PROC PRINT;
 VAR SID D SAMDR RANK_ID;
PROC MEANS MEAN N STD MIN MAX RANGE;
 VAR SAMDR;
RUN;
```

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Appendix J: Scree Plot Identifying Outliers for Hypothesis One

Figure 2.

Scree plot for studies reporting the effects of acute stress measured at

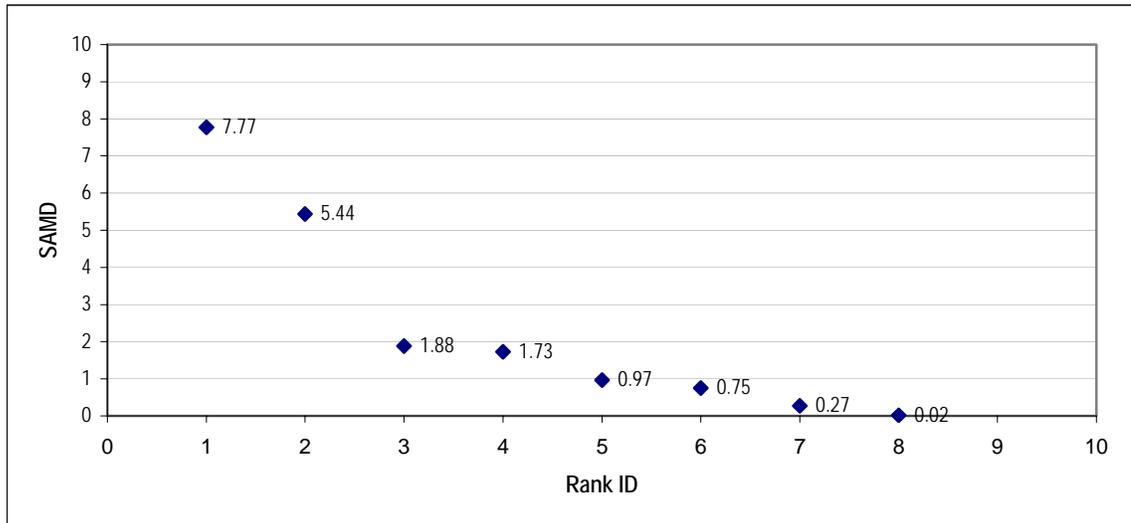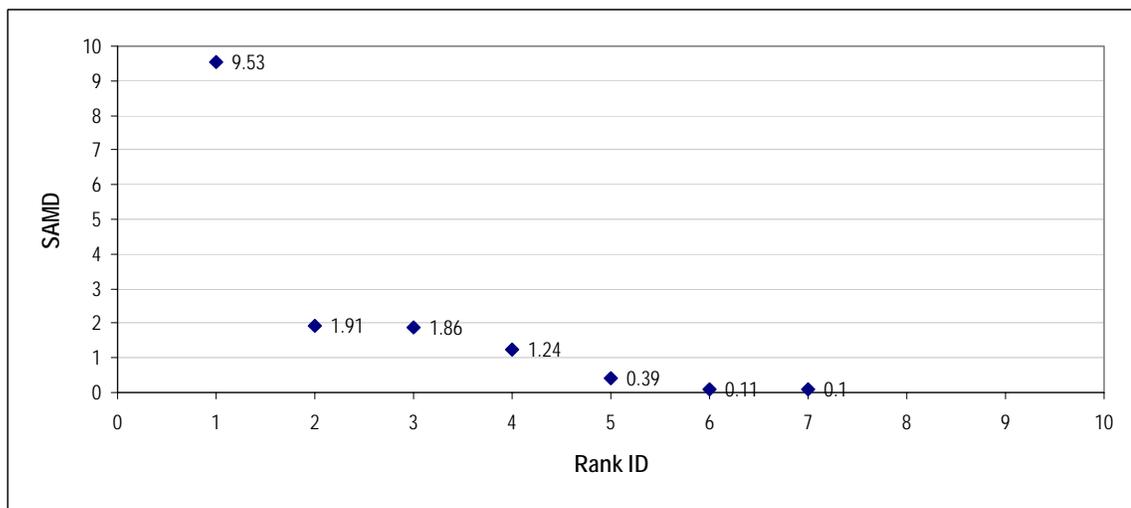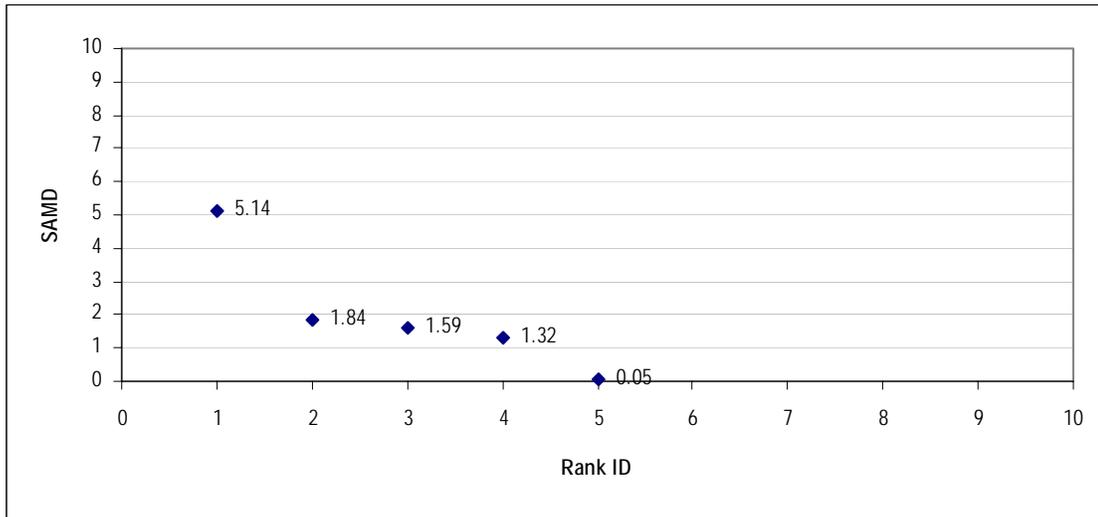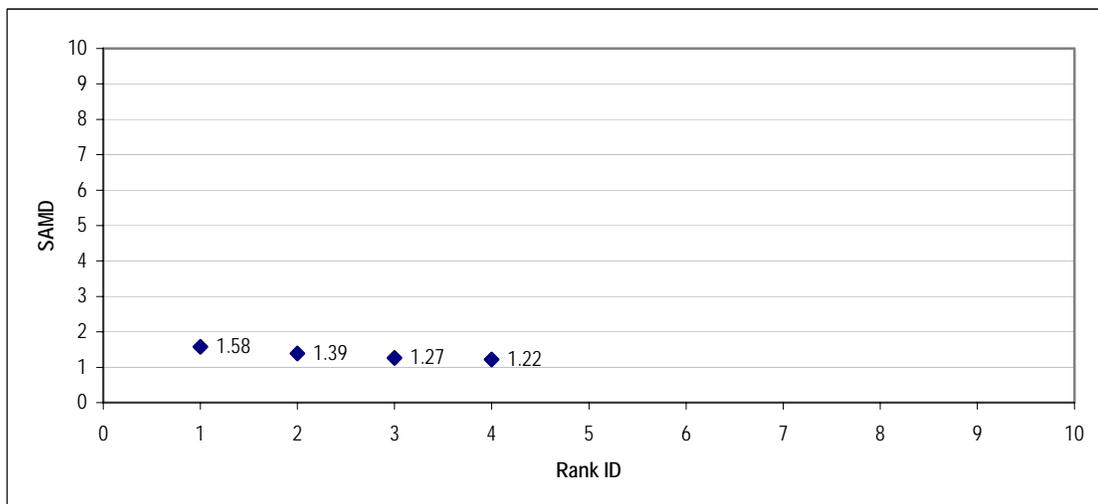*baseline/pre-treatment on ART treatment outcomes*

Figure 3.

Scree plot for studies reporting the effects of chronic stress measured at

baseline/pre-treatment on ART treatment outcomes

Figure 4.

Scree plot for studies reporting the effects of depression measured at

baseline/pre-treatment *on ART treatment outcomes*

Figure 5.

Scree plot for studies reporting the effects of acute stress measured during the

follicular phase *on ART treatment outcomes*

Figure 6.

Scree plot for studies reporting the effects of chronic stress measured during the
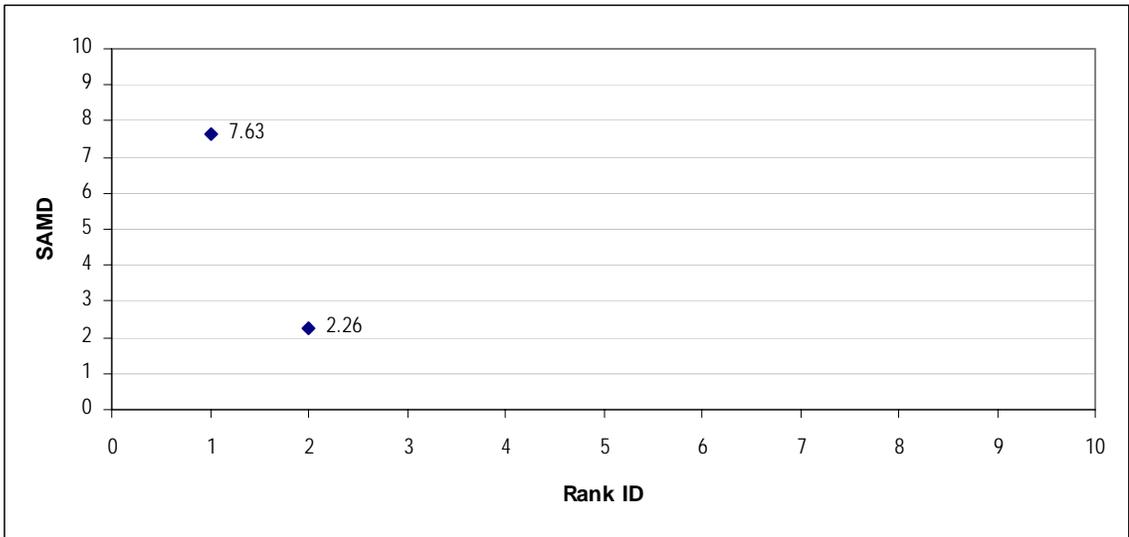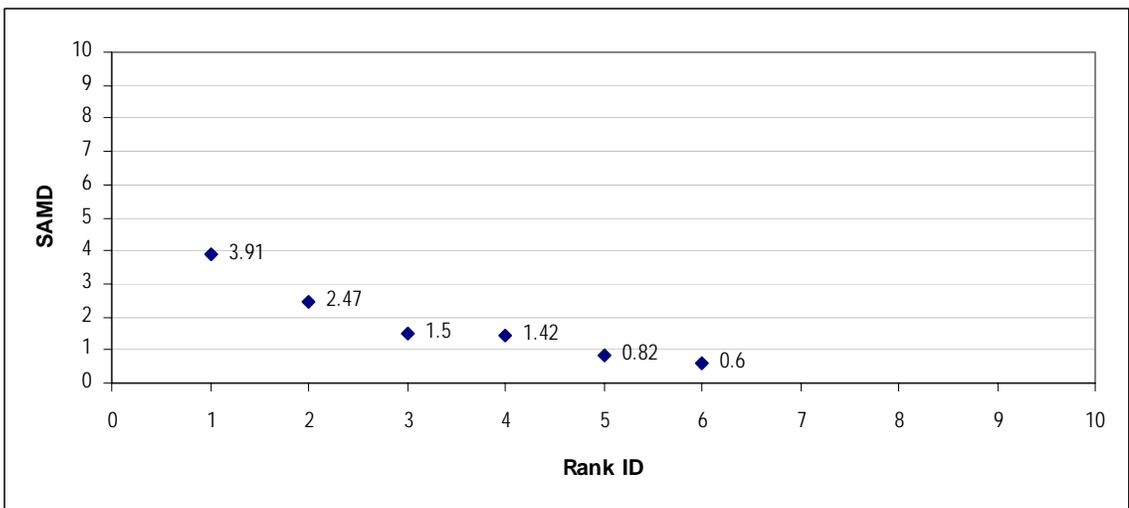
follicular phase *on ART treatment outcomes*

Figure 7.

Scree plot for studies reporting the effects of acute stress measured during

oocyte retrieval *on ART treatment outcomes*

Figure 8.

Scree plot for studies reporting the effects of chronic stress measured during
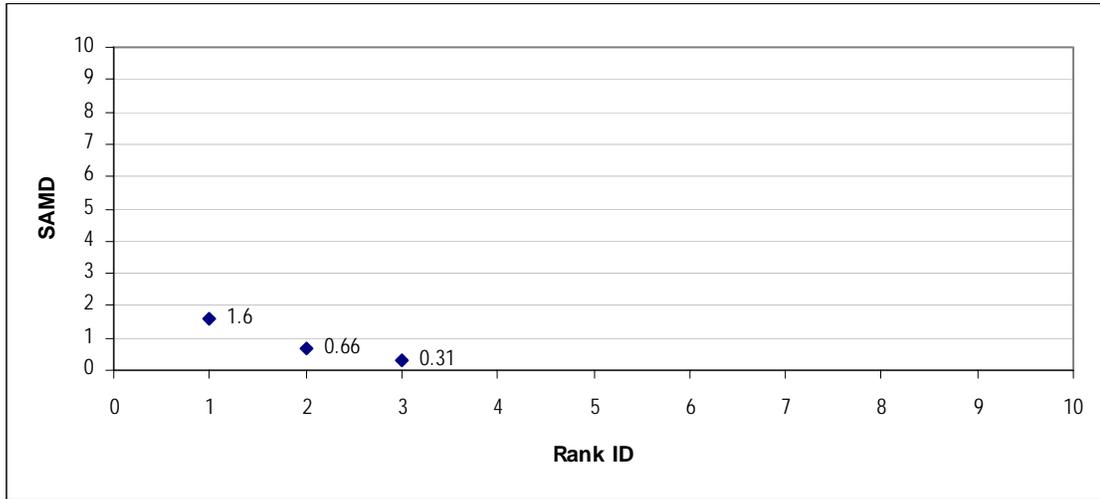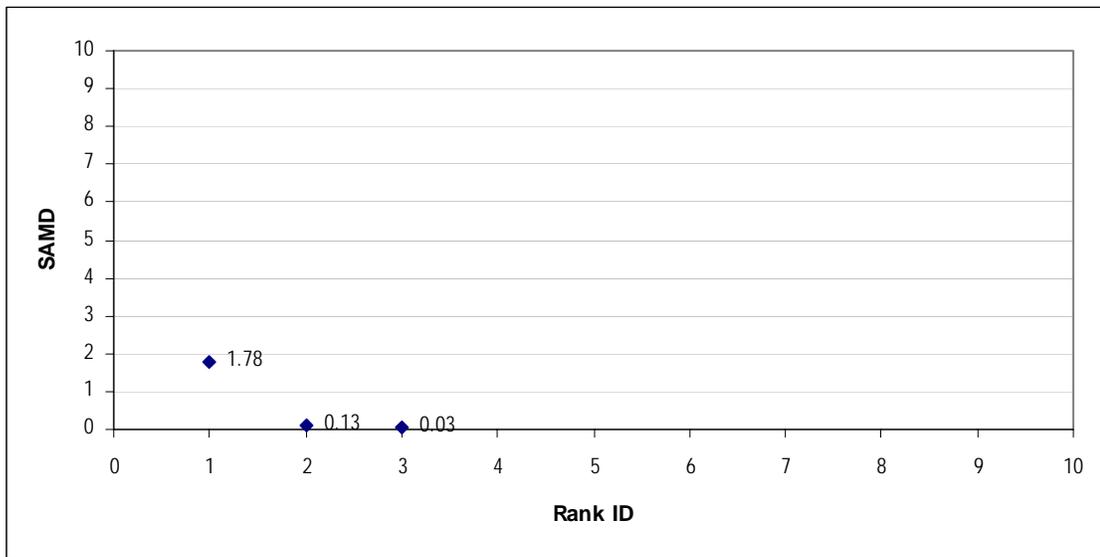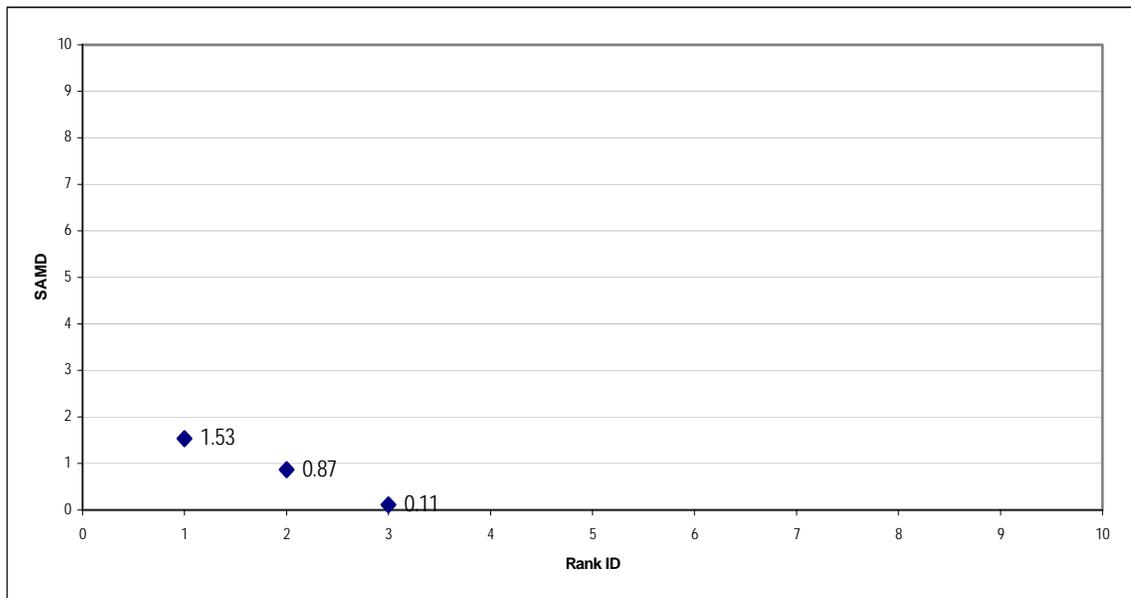
oocyte retrieval on ART treatment outcomes

Figure 9.

Scree plot for studies reporting the effects of acute stress measured at embryo

transfer on ART treatment outcomes

Figure 10.

Scree plot for studies reporting the effects of acute stress measured during the

luteal phase on ART treatment outcomes

Appendix K: SAS Code for HLM Regression Analysis for Hypothesis One

```
TITLE1 'REGRESSION ANALYSIS INCLUDING OUTLIERS';
DATA ONE;
INPUT SID 1-2 TI 4-9 .3 VI 11-17 .5 T1 19 T2 21 T3 23 T4 25 T5 27 C1 29
C2 31 C3 33;
WI = 1 / VI;
CARDS;
03 -0.071 0.10236 1 0 0 0 0 1 0 0
06  1.412 0.03949 1 0 0 0 0 1 0 0
08 -0.630 0.01718 1 0 0 0 0 1 0 0
09  0.199 0.03716 1 0 0 0 0 1 0 0
11  0.498 0.07513 1 0 0 0 0 1 0 0
12  0.865 0.20504 1 0 0 0 0 1 0 0
13  0.241 0.09340 1 0 0 0 0 1 0 0
28  0.024 0.05459 1 0 0 0 0 1 0 0
03  0.190 0.10275 1 0 0 0 0 0 1 0
06  1.787 0.04384 1 0 0 0 0 0 1 0
08 -0.061 0.01655 1 0 0 0 0 0 1 0
11  0.579 0.07591 1 0 0 0 0 0 1 0
13  0.629 0.09684 1 0 0 0 0 0 1 0
20  0.048 0.05460 1 0 0 0 0 0 1 0
28  0.050 0.05460 1 0 0 0 0 0 1 0
06  0.949 0.03553 1 0 0 0 0 0 0 1
08 -0.117 0.01657 1 0 0 0 0 0 0 1
09  0.326 0.03742 1 0 0 0 0 0 0 1
25  0.041 0.05682 1 0 0 0 0 0 0 1
28 -0.332 0.05508 1 0 0 0 0 0 0 1
03  0.573 0.10641 0 1 0 0 0 1 0 0
12  0.598 0.19616 0 1 0 0 0 1 0 0
14  0.473 0.13613 0 1 0 0 0 1 0 0
20 -0.212 0.05479 0 1 0 0 0 1 0 0
14  2.723 0.22602 0 1 0 0 0 0 0 1
20 -0.328 0.05507 0 1 0 0 0 0 0 1
01  0.459 0.12803 0 0 1 0 0 1 0 0
03  0.806 0.11042 0 0 1 0 0 1 0 0
10 -0.616 0.03344 0 0 1 0 0 1 0 0
13  0.437 0.09475 0 0 1 0 0 1 0 0
14  0.190 0.13378 0 0 1 0 0 1 0 0
20 -0.177 0.05473 0 0 1 0 0 1 0 0
01  0.080 0.12547 0 0 1 0 0 0 1 0
10  0.034 0.03249 0 0 1 0 0 0 1 0
20 -0.306 0.05500 0 0 1 0 0 0 0 1
03  0.643 0.10747 0 0 0 1 0 1 0 0
14  0.000 0.13333 0 0 0 1 0 1 0 0
20  0.065 0.05461 0 0 0 1 0 1 0 0
20  0.067 0.05461 0 0 0 1 0 0 0 1
03  0.866 0.11168 0 0 0 0 1 1 0 0
12  1.528 0.24110 0 0 0 0 1 1 0 0
20  0.107 0.05464 0 0 0 0 1 1 0 0
20 -0.007 0.05459 0 0 0 0 1 0 0 1;
```

Appendix K: (Continued)

```
PROC MIXED COVTEST CL;
 CLASS SID;
 MODEL TI = T1 T2 T3 T4 T5 C1 C2 C3 / SOLUTION DDFM = BW NOTEST CL;
WEIGHT WI;
 RANDOM INTERCEPT / SUB = SID;
RUN;
```

Appendix L: SAS Code for Null Model HLM Analysis for Hypothesis One

```
TITLE1 'REGRESSION ANALYSIS INCLUDING OUTLIERS';
DATA ONE;
INPUT SID 1-2 TI 4-9 .3 VI 11-17 .5 T1 19 T2 21 T3 23 T4 25 T5 27 C1 29
C2 31 C3 33;
WI = 1 / VI;
CARDS;
03 -0.071 0.10236 1 0 0 0 0 1 0 0
06  1.412 0.03949 1 0 0 0 0 1 0 0
08 -0.630 0.01718 1 0 0 0 0 1 0 0
09  0.199 0.03716 1 0 0 0 0 1 0 0
11  0.498 0.07513 1 0 0 0 0 1 0 0
12  0.865 0.20504 1 0 0 0 0 1 0 0
13  0.241 0.09340 1 0 0 0 0 1 0 0
28  0.024 0.05459 1 0 0 0 0 1 0 0
03  0.190 0.10275 1 0 0 0 0 0 1 0
06  1.787 0.04384 1 0 0 0 0 0 1 0
08 -0.061 0.01655 1 0 0 0 0 0 1 0
11  0.579 0.07591 1 0 0 0 0 0 1 0
13  0.629 0.09684 1 0 0 0 0 0 1 0
20  0.048 0.05460 1 0 0 0 0 0 1 0
28  0.050 0.05460 1 0 0 0 0 0 1 0
06  0.949 0.03553 1 0 0 0 0 0 0 1
08 -0.117 0.01657 1 0 0 0 0 0 0 1
09  0.326 0.03742 1 0 0 0 0 0 0 1
25  0.041 0.05682 1 0 0 0 0 0 0 1
28 -0.332 0.05508 1 0 0 0 0 0 0 1
03  0.573 0.10641 0 1 0 0 0 1 0 0
12  0.598 0.19616 0 1 0 0 0 1 0 0
14  0.473 0.13613 0 1 0 0 0 1 0 0
20 -0.212 0.05479 0 1 0 0 0 1 0 0
14  2.723 0.22602 0 1 0 0 0 0 0 1
20 -0.328 0.05507 0 1 0 0 0 0 0 1
01  0.459 0.12803 0 0 1 0 0 1 0 0
03  0.806 0.11042 0 0 1 0 0 1 0 0
10 -0.616 0.03344 0 0 1 0 0 1 0 0
13  0.437 0.09475 0 0 1 0 0 1 0 0
14  0.190 0.13378 0 0 1 0 0 1 0 0
20 -0.177 0.05473 0 0 1 0 0 1 0 0
01  0.080 0.12547 0 0 1 0 0 0 1 0
10  0.034 0.03249 0 0 1 0 0 0 1 0
20 -0.306 0.05500 0 0 1 0 0 0 0 1
03  0.643 0.10747 0 0 0 1 0 1 0 0
14  0.000 0.13333 0 0 0 1 0 1 0 0
20  0.065 0.05461 0 0 0 1 0 1 0 0
20  0.067 0.05461 0 0 0 1 0 0 0 1
03  0.866 0.11168 0 0 0 0 1 1 0 0
12  1.528 0.24110 0 0 0 0 1 1 0 0
20  0.107 0.05464 0 0 0 0 1 1 0 0
20 -0.007 0.05459 0 0 0 0 1 0 0 1
;
PROC MIXED COVTEST CL;
CLASS SID;
```

```
 MODEL TI = / SOLUTION DDFM = BW NOTEST CL;
WEIGHT WI;
 RANDOM INTERCEPT / SUB = SID;
RUN;
```

Appendix M: SAS Code for Moderator Analysis for Hypothesis One –

Duration of Infertility

```
TITLE1 'REGRESSION MODERATOR ANALYSIS INCLUDING OUTLIERS';
DATA ONE;
INPUT SID 1-2 TI 4-9 .3 VI 11-17 .5 DURATION 19-21 .1 NA 23 SWA 25 AUSI
27 SEA 29 EURO 31;
WI = 1 / VI;
CARDS;
03 -0.071 0.10236 4.4 1 0 0 0 0
06  1.412 0.03949 5.5 0 0 0 1 0
08 -0.630 0.01718     0 0 1 0 0
09  0.199 0.03716 3.7 0 0 0 0 1
11  0.498 0.07513     0 0 1 0 0
12  0.865 0.20504     0 0 0 0 1
13  0.241 0.09340 6.3 0 0 0 0 1
28  0.024 0.05459 6.9 0 1 0 0 0
03  0.190 0.10275 6.1 0 0 0 0 1
06  1.787 0.04384 5.5 0 0 0 1 0
08 -0.061 0.01655     0 0 1 0 0
11  0.579 0.07591     0 0 1 0 0
13  0.629 0.09684 6.3 0 0 0 0 1
20  0.048 0.05460     0 1 0 0 0
28  0.050 0.05460 6.9 0 1 0 0 0
06  0.949 0.03553 5.5 0 0 0 1 0
08 -0.117 0.01657     0 0 1 0 0
09  0.326 0.03742 3.7 0 0 0 0 1
25  0.041 0.05682 4.1 0 0 0 0 1
28 -0.332 0.05508 6.9 0 1 0 0 0
03  0.573 0.10641 4.4 1 0 0 0 0
12  0.598 0.19616     0 0 0 0 1
14  0.473 0.13613 6.1 0 0 0 0 1
20 -0.212 0.05479     0 1 0 0 0
14  2.723 0.22602 6.1 0 0 0 0 1
20 -0.328 0.05507     0 1 0 0 0
01  0.459 0.12803     0 0 0 0 1
03  0.806 0.11042 4.4 1 0 0 0 0
10 -0.616 0.03344 6.1 0 0 0 0 1
13  0.437 0.09475 6.3 0 0 0 0 1
14  0.190 0.13378 6.1 0 0 0 0 1
20 -0.177 0.05473     0 1 0 0 0
01  0.080 0.12547     0 0 0 0 1
10  0.034 0.03249 6.1 0 0 0 0 1
20 -0.306 0.05500     0 1 0 0 0
03  0.643 0.10747 4.4 1 0 0 0 0
14  0.000 0.13333 6.1 0 0 0 0 1
20  0.065 0.05461     0 1 0 0 0
20  0.067 0.05461     0 1 0 0 0
03  0.866 0.11168 4.4 1 0 0 0 0
12  1.528 0.24110     0 0 0 0 1
20  0.107 0.05464     0 1 0 0 0
20 -0.007 0.05459     0 1 0 0 0;
```

```
PROC MIXED COVTEST CL;
CLASS SID;
MODEL TI = DURATION / SOLUTION DDFM = BW NOTEST CL;
 WEIGHT WI;
 RANDOM INTERCEPT / SUB = SID;
RUN;
```

Appendix N: SAS Code for Moderator Analysis for Hypothesis One –

Country of Study Origin

```
TITLE1 'REGRESSION MODERATOR ANALYSIS INCLUDING OUTLIERS';
DATA ONE;
INPUT SID 1-2 TI 4-9 .3 VI 11-17 .5 DURATION 19-21 .1 NA 23 SWA 25 AUSI
27 SEA 29 EURO 31;
WI = 1 / VI;
CARDS;
03 -0.071 0.10236 4.4 1 0 0 0 0
06  1.412 0.03949 5.5 0 0 0 1 0
08 -0.630 0.01718     0 0 1 0 0
09  0.199 0.03716 3.7 0 0 0 0 1
11  0.498 0.07513     0 0 1 0 0
12  0.865 0.20504     0 0 0 0 1
13  0.241 0.09340 6.3 0 0 0 0 1
28  0.024 0.05459 6.9 0 1 0 0 0
03  0.190 0.10275 6.1 0 0 0 0 1
06  1.787 0.04384 5.5 0 0 0 1 0
08 -0.061 0.01655     0 0 1 0 0
11  0.579 0.07591     0 0 1 0 0
13  0.629 0.09684 6.3 0 0 0 0 1
20  0.048 0.05460     0 1 0 0 0
28  0.050 0.05460 6.9 0 1 0 0 0
06  0.949 0.03553 5.5 0 0 0 1 0
08 -0.117 0.01657     0 0 1 0 0
09  0.326 0.03742 3.7 0 0 0 0 1
25  0.041 0.05682 4.1 0 0 0 0 1
28 -0.332 0.05508 6.9 0 1 0 0 0
03  0.573 0.10641 4.4 1 0 0 0 0
12  0.598 0.19616     0 0 0 0 1
14  0.473 0.13613 6.1 0 0 0 0 1
20 -0.212 0.05479     0 1 0 0 0
14  2.723 0.22602 6.1 0 0 0 0 1
20 -0.328 0.05507     0 1 0 0 0
01  0.459 0.12803     0 0 0 0 1
03  0.806 0.11042 4.4 1 0 0 0 0
10 -0.616 0.03344 6.1 0 0 0 0 1
13  0.437 0.09475 6.3 0 0 0 0 1
14  0.190 0.13378 6.1 0 0 0 0 1
20 -0.177 0.05473     0 1 0 0 0
01  0.080 0.12547     0 0 0 0 1
10  0.034 0.03249 6.1 0 0 0 0 1
20 -0.306 0.05500     0 1 0 0 0
03  0.643 0.10747 4.4 1 0 0 0 0
14  0.000 0.13333 6.1 0 0 0 0 1
20  0.065 0.05461     0 1 0 0 0
20  0.067 0.05461     0 1 0 0 0
03  0.866 0.11168 4.4 1 0 0 0 0
12  1.528 0.24110     0 0 0 0 1
20  0.107 0.05464     0 1 0 0 0
20 -0.007 0.05459     0 1 0 0 0;
```

```
PROC MIXED COVTEST CL;
CLASS SID;
MODEL TI = NA SWA AUSI SEA EURO / SOLUTION DDFM = BW NOTEST CL;
 WEIGHT WI;
 RANDOM INTERCEPT / SUB = SID;
RUN;
```

Appendix O: SAS Code for Combining Effect Sizes for Hypothesis Two

```
TITLE 'COMBINING STANDARDIZED MEAN DIFFERENCES BY CONSTRUCT';
DATA ORIG;
 INPUT ID 1 CONSTRUCT 3 D 5-11 N1 13-14 N2 16-17 QI 19-21 .2;
*     +-----------------------------------+
         COMPUTE CI FOR EACH STUDY
      +-----------------------------------+;
V=((N1+N2)/(N1*N2))+((D**2)/(2*(N1+N2)));
LOWER = D - (1.96*SQRT(V));
UPPER = D + (1.96*SQRT(V));
*     +--------------------------------------------------+
         WEIGHT STUDIES BY QUALITY INDEX & SAMPLE SIZE
      +--------------------------------------------------+;
W = 1/V;
QISQ = QI**2;
QIW = QI*W;
QISQW = QISQ*W;
QIWD = QI*W*D;
DSQ = D**2;
WDSQ = W*DSQ;
WD = W*D;
WSQ = W**2;
N = N1 + N2;
CARDS;
1 1 0.37830 37 45 .92
1 3 1.16280 37 45 .92
2 1 0.31820 24 49 .62
2 1 0.25820 24 49 .62
2 2 -0.2818 24 49 .62
2 2 0.18540 24 49 .62
2 3 0.45640 24 49 .62
2 3 0.20060 24 49 .62
3 1 0.79600 26 19 .91
3 3 0.09640 26 19 .91
4 1 0.59420 30 30 .77
4 3 1.29320 30 30 .76
;
DATA FIRST;
 SET ORIG;
 IF CONSTRUCT = 1;
PROC PRINT DATA = FIRST;
 TITLE 'SUMMARY STATISTICS FOR D';
 VAR ID D V N CONSTRUCT LOWER UPPER QI W QISQW QIW QIWD WDSQ WD;
PROC MEANS SUM N DATA = FIRST;
 VAR N W WSQ WDSQ WD;
*     +------------------------------------------------+
         WRITE OUT SUMMARY STATISTICS FOR VARIANCES
      +------------------------------------------------+;
OUTPUT OUT = COMBINE
SUM = Total_N SW SWSQ SWDSQ SWD
MEAN = MNN
```

```
N = N1;
PROC PRINT;
VAR SW SWSQ SWDSQ SWD MNN N1;
DATA COMBINE;
 SET COMBINE;
*      +----------------------------------------------+
          COMPUTE UNCONDITIONAL VARIANCE COMPONENT
       +----------------------------------------------+;
C = (SW -((SWSQ/SW)));
Q = SWDSQ - ((SWD**2)/SW);
* Karen: This computes the probability associated with Q;
Prob_Q = 1 - probchi(Q, N1 - 1);
DF = N1 -1;
BTWNV = (Q - (N1 - 1))/C;
EQ = C*BTWNV + (N1 -1);
PROC PRINT;
 VAR C Q DF PROB_Q BTWNV EQ;
*      +----------------------------------------------+
             COMPUTE TOTAL WEIGHTED VARIANCE
       +----------------------------------------------+;
DATA TWO;
 IF _N_ = 1 THEN SET COMBINE;
 SET FIRST;
WW = 1/(BTWNV + V);
WV1 = QISQ*WW;
WV2 = QI*WW;
WV2B = WV2**2;
IWV = WV1 / WV2B;
WQIWD = QI*WW*D;
PROC PRINT;
 TITLE 'SUMMARY STATISTICS FOR WEIGHTED D UNDER RANDOM EFFECTS MODEL';
 VAR ID D V LOWER UPPER IWV QI W WW WV1 WV2 WV2B WQIWD C Q BTWNV EQ;
 PROC MEANS SUM N;
  VAR N WW WV1 WV2 WQIWD;
*      +----------------------------------------------+
          WRITE OUT SUMMARY STATISTICS TO COMBINE
       +----------------------------------------------+;
OUTPUT OUT = RESULTS
SUM = Total_N SWW SWV1 SWV2 SWQIWD
MEAN = MNN
N = N1 N2 N3;
DATA REFINAL;
 SET RESULTS;
DPLUS = SWQIWD/SWV2;
WWV = SWV1/(SWV2**2);
VERROR = ((MNN-1)/(MNN-3))*(4/MNN)*(1+((DPLUS**2)/8));
UNBIASV = WWV - VERROR;
IF UNBIASV LT 0 THEN UNBIASV = 0;
A = 1+(0.75/(MNN-3));
SE = SQRT(WWV);
DPLUSC = DPLUS/A;
SEC = SE/A;
```

```
CLL = DPLUSC - (1.96*SEC);
CUL = DPLUSC + (1.96*SEC);
PROC PRINT;
VAR SWV1 SWV2 WWV VERROR UNBIASV MNN A SE DPLUS DPLUSC SEC;
PROC PRINT;
TITLE 'RANDOM EFFECTS WEIGHTED AVERAGE D AND VARIANCE';
 VAR DPLUSC SEC CLL CUL;
RUN;
```

Appendix P: SAS Code for Computing SAMD Statistic for Hypothesis Two

```
DATA ONE;
 INPUT ID 1 CONSTRUCT 3 D 5-11 N1 13-14 N2 16-17 QI 19-21 .2;
V = ((N1 +N2)/(N1*N2)+((D**2)/(2*N1+N2)));
W = 1/V;
N = N1 + N2;
DN = D*W;
CARDS;
1 1 0.37830 37 45 .92
1 3 1.16280 37 45 .92
2 1 0.31820 24 49 .62
2 1 0.25820 24 49 .62
2 2 -0.2818 24 49 .62
2 2 0.18540 24 49 .62
2 3 0.45640 24 49 .62
2 3 0.20060 24 49 .62
3 1 0.79600 26 19 .91
3 3 0.09640 26 19 .91
4 1 0.59420 30 30 .77
4 3 1.29320 30 30 .76
;
PROC SORT;
 BY CONSTRUCT;
DATA TC;
 SET ONE;
 IF CONSTRUCT EQ 3;
PROC MEANS MEAN MAXDEC = 2;
 VAR D;
PROC MEANS SUM MAXDEC = 2;
 VAR DN;
PROC MEANS MEAN SUM N MAXDEC = 2;
 VAR N;
DATA TWO;
 SET TC;
MEAN_D = .64;
TOTAL_D = 45.73;
MEAN_N = 66.6;
TOTAL_N = 333;
K = 5;
* +---------------------------------------------+
    COMPUTATIONS EXCLUDING INDIVIDUAL STUDIES
  +---------------------------------------------+;
TOTAL_NW = TOTAL_N - N;
MEAN_DW = (TOTAL_D - DN)/TOTAL_NW;
VAR_I = (4*(N-1)*(1+((MEAN_DW**2)/8)))/(N*(N-3));
VAR_D = (4*(MEAN_N-1)*(1+((MEAN_DW**2)/8)))/(MEAN_N*(MEAN_N-3)*K);
SAMD_I = (D-MEAN_DW)/(SQRT(VAR_I+VAR_D));
SAMD = ABS(SAMD_I);
SAMDR = ROUND (SAMD,.01);
```

```
* +-----------------------------------------------+
     RANK ORDERS THE SAMD FOR EACH STUDY
  +-----------------------------------------------+;
PROC RANK DESCENDING OUT = TEMP;
VAR SAMDR;
RANKS RANK_ID;
PROC SORT;
 BY RANK_ID;
DATA THREE;
 SET TEMP;
FILE OUTPUT;
 PUT RANK_ID SAMDR;
PROC PRINT;
 VAR ID D SAMDR RANK_ID;
PROC MEANS MEAN N STD MIN MAX RANGE;
 VAR SAMDR;
RUN
;
```

Appendix Q: Scree Plot Identifying Outliers for Hypothesis Two

Figure 13.

Scree plot for studies reporting the effects of psychoeducational interventions on acute stress experienced during ART treatment regimens
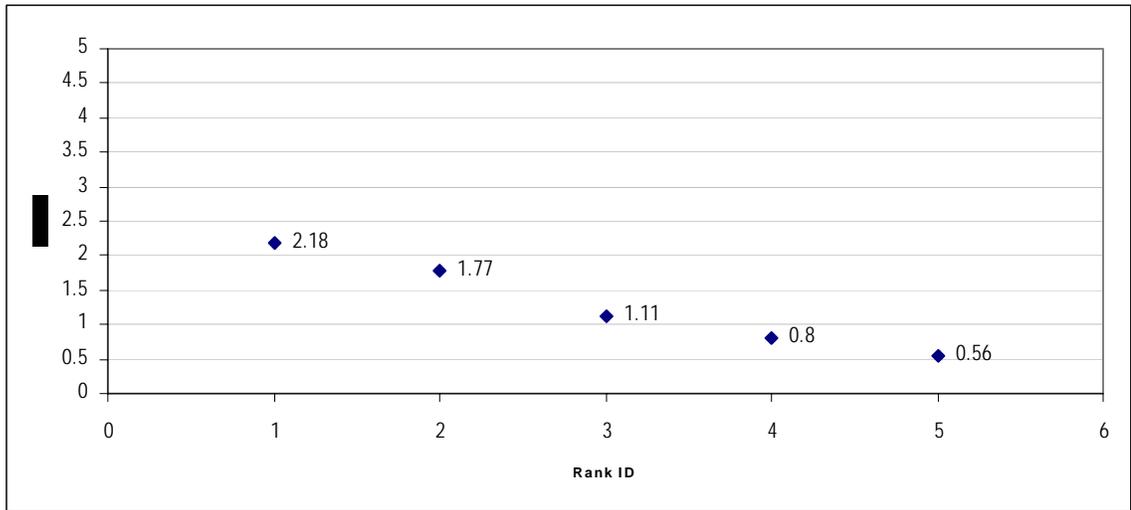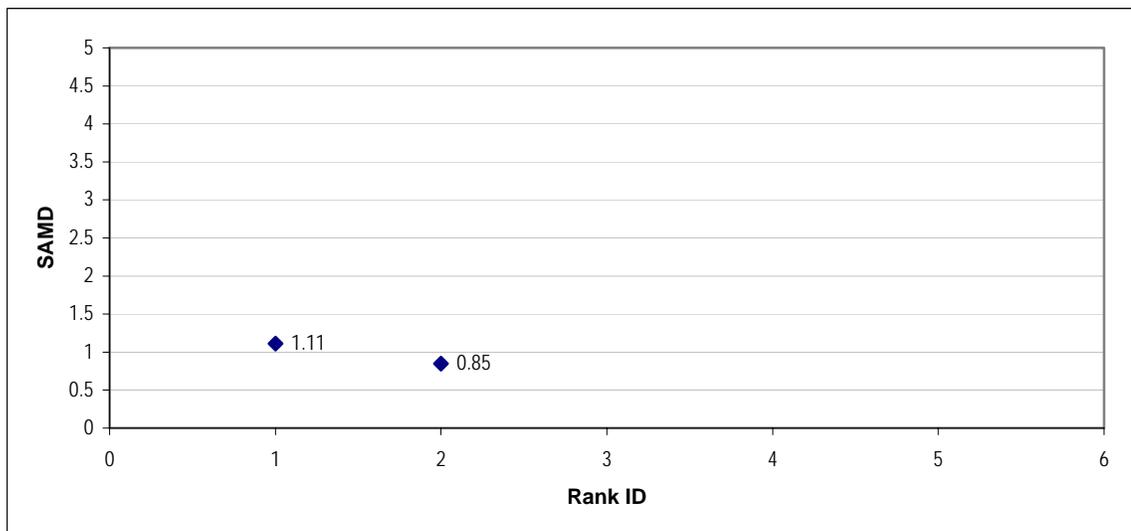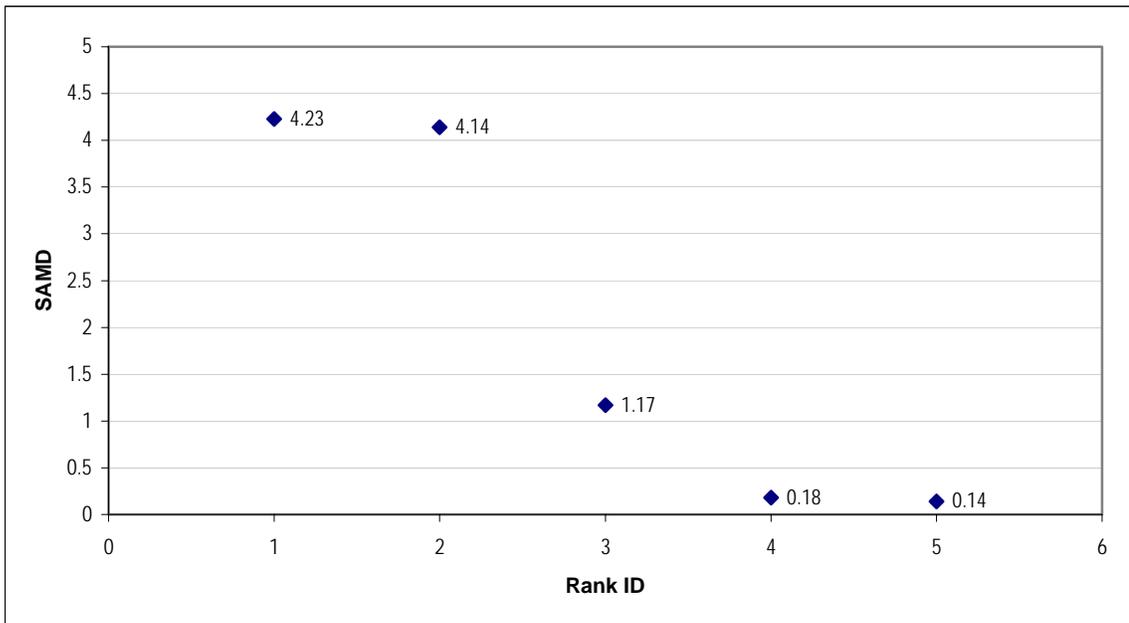

Figure 14.

Scree plot for studies reporting the effects of psychoeducational interventions on chronic stress experienced during ART treatment regimens

Figure 15.

Scree plot for studies reporting the effects of psychoeducational interventions on depression experienced during ART treatment regimens

Appendix R: SAS Code for HLM Regression Analysis for Hypothesis Two

```
TITLE1 'HYPOTHESIS TWO REGRESSION ANALYSIS INCLUDING OUTLIERS';
DATA ONE;
INPUT SID 1 TI 3-9 .3 VI 11-18 .5 C1 20 C2 22 C3 24;
WI = 1/VI;
CARDS;
1 0.37830 0.050122 1 0 0
2 0.31820 0.062768 1 0 0
2 0.25820 0.062531 1 0 0
2 -0.2818 0.062619 0 1 0
2 0.18540 0.062310 0 1 0
2 0.45640 0.063502 0 0 1
2 0.20060 0.062350 0 0 1
3 0.79600 0.098133 1 0 0
3 0.09640 0.091196 0 0 1
4 0.59420 0.069609 1 0 0
1 1.16280 0.057494 0 0 1
4 1.29320 0.080603 0 0 1
;
PROC MIXED COVTEST CL;
 CLASS SID;
 MODEL TI = C1 C2 C3 / SOLUTION DDFM = BW NOTEST CL;
 WEIGHT WI;
 RANDOM INTERCEPT / SUB = SID;
RUN;
```

Appendix S: SAS Code for Null Model HLM Regression Analysis for

Hypothesis Two

```
TITLE1 'HYPOTHESIS TWO REGRESSION ANALYSIS NULL MODEL INCLUDING
OUTLIERS';
DATA ONE;
INPUT SID 1 TI 3-9 .3 VI 11-18 .5 C1 20 C2 22 C3 24;
WI = 1/VI;
CARDS;
1 0.37830 0.050122 1 0 0
2 0.31820 0.062768 1 0 0
2 0.25820 0.062531 1 0 0
2 -0.2818 0.062619 0 1 0
2 0.18540 0.062310 0 1 0
2 0.45640 0.063502 0 0 1
2 0.20060 0.062350 0 0 1
3 0.79600 0.098133 1 0 0
3 0.09640 0.091196 0 0 1
4 0.59420 0.069609 1 0 0
1 1.16280 0.057494 0 0 1
4 1.29320 0.080603 0 0 1
;
PROC MIXED COVTEST CL;
 CLASS SID;
 MODEL TI = / SOLUTION DDFM = BW NOTEST CL;
 WEIGHT WI;
 RANDOM INTERCEPT / SUB = SID;
RUN;
```

ABOUT THE AUTHOR

Karen Rose Mumford has spent her professional career as an educator. Beginning in 1992, she began her career as a teacher, working with children with severe emotional disturbances and later with children with autism. As a teacher, Karen is known for her unique teaching strategies and techniques. Recognized as an educational leader, Karen accepted an administrative position as Coordinator of Evaluation in 2000. In this position, Karen provides data and information related to program effectiveness, improving the educational opportunities and achievements of students.

Karen received her bachelor's degree in special education and her master's degree in Educational Leadership. After marrying, Karen received her doctoral degree from the University of South Florida in Educational Measurement and Research. Along with her co-authors, she was awarded the "Distinguished Paper of the Florida Educational Research Association" in 2001. Karen plans to continue conducting research in health related issues and teach at the university level.