Title

Risk of Preterm Delivery and Low Birth Weight In Singleton Pregnancies Conceived By Women With and Without a History of Infertility

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RISK OF PRETERM DELIVERY AND LOW BIRTH WEIGHT IN SINGLETON PREGNANCIES CONCEIVED BY WOMEN WITH AND WITHOUT A HISTORY OF INFERTILITY

by

Loretta Camarano

DISSERTATION

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To Stanley,
your love and support
made this work possible

RISK OF PRETERM DELIVERY AND LOW BIRTH WEIGHT
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ABSTRACT

Aims: The objective of this study was to determine predictors of low birth weight (LBW) and preterm delivery (PTD) in singleton pregnancies conceived by women with a history of infertility compared to singleton pregnancies conceived spontaneously by fertile woman.

Methods: Data were collected at eleven infertility clinics in Northern California. Using a retrospective cohort design, record review was conducted on women who carried singleton pregnancies to ≥ 20 weeks gestation between 1994 and 1998. These women were stratified by method of conception: women who conceived using infertility treatment (n=542), women who conceived naturally following a history of infertility (n=441), and fertile women (n= 1008) identified through California Vital Statistics records. Logistic regression was used to determine whether an association exists between LBW or PTD and infertility or infertility treatment compared to fertile women, controlling for potential confounding variables.

Results: There was no significant difference in the frequency of PTD between the three groups of women; however there was a significant difference in the frequency of LBW between the three groups of women ($p < .05$). 10.8 % of women in the infertile treatment group, 8.6% of women in the infertile without treatment group and 6.4% of women in the fertile group delivered a LBW infant. Women with a history of infertility who had treatment were 1.55 (CI 1.03, 2.34) times more likely to have a LBW infant compared to

the fertile group controlling for maternal age, nulliparity, gestational diabetes, and obesity. There was no significant increased odds of delivery of a LBW infant for the infertile without treatment group compared to the fertile group, controlling for maternal age, nulliparity, gestational diabetes, and obesity. Nulliparity was a significant independent predictor of LBW (OR 1.51, CI 1.07, 2.14) in all three groups when controlling for maternal age, gestational diabetes and obesity regardless of fertility conception status.

Conclusion: Women with a history of infertility who undergo infertility treatment and conceive a singleton pregnancy are not at increased risk of preterm delivery but may be at increased risk for having a LBW infant.

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CHAPTER 1 THE STUDY PROBLEM

Introduction

Infertility is defined as the inability of a couple to achieve conception after one year of unprotected intercourse (Speroff & Fritz, 2005). Infertility incidence rates range from 10% to 20% of American couples of childbearing age (Guzick & Swan, 2006; Speroff & Fritz, 2005). Etiology of a couple's infertility may be found in either the male or female partner. Infertility due to female factors occurs in 30% to 40% of cases, while infertility due to male factors occurs in 10% to 30% of cases, and infertility problems diagnosed in both partners occurs in 15% to 30% of cases (Adamson & Baker, 2003; Speroff & Fritz, 2005). Also, the relatively recent practice of delaying childbearing until a couple is in their thirties, forties, or even fifties contributes to infertility. Many couples feel that they are more stable and financially prepared to assume the responsibilities of parenting at this later stage of life; however, women and men enter a period of decreasing fertility as they enter middle adulthood (Balen & Rutherford, 2007).

Most couples expect they will conceive once they decide to have a child (Mahlstedt, 1985). The awareness of a fertility problem begins to emerge when one or both of the partners begin to wonder why they are not yet pregnant. Once a concern about delayed conception has been identified, about half of all American couples experiencing infertility will pursue medical assessment and treatment (Boivin, Bunting, Collins, & Nygren, 2007). Evaluation for infertility begins with a sequence of tests for both partners. This may suggest or reveal a cause for the infertility. Even after the cause of infertility has been diagnosed, however, there is no guarantee that treatment will be

successful. Standard treatment for infertility consists of surgery to correct disorders of the reproductive organs, medications to treat ovulatory dysfunction and induce multiple egg development in women and/or intrauterine insemination (IUI) with sperm from the male partner or from a donor. Additionally, there is an assisted reproductive technology (ART) treatment known as in vitro fertilization (IVF). The American Society for Reproductive Medicine defines ART as treatments and procedures that handle the human oocytes and sperm outside the body for the purpose of establishing a pregnancy. IVF involves ovarian stimulation with medications, egg retrieval from the woman, and sperm collection from the man before fertilization takes place in a Petri dish (i.e., in vitro). The fertilized eggs are then transferred into the woman's uterus several days later where implantation and embryo development may occur just as they would in a spontaneous conception.

IVF, an experimental procedure developed in 1978 to treat women with fallopian tube damage (Steptoe & Edwards, 1978), is now a readily available treatment for almost all known causes of infertility and accounts for 96% of all assisted reproductive technology (ART) procedures performed in the United States (U.S.) (ASRM, 2007; Katz, Nachtigall, & Showstack, 2002). The most recent report from the Society for Assisted Reproductive Technology (SART) and the ASRM states that at least 385 clinics were performing ART as of 2001 in the U.S. (ASRM, 2007). These clinics performed 79,042 cycles of IVF with a pregnancy delivery rate of 31.6% per IVF procedure. In the U.S., 21,475 deliveries, of which 35.8% were multiple-gestation pregnancies, were reported to be the result of IVF procedures performed in 2001 alone. It is estimated that nearly 1% of all births in the U.S. are the result of conceptions due to IVF (Burry, 2007). The most

recent collaborative report on IVF issued by the International Committee for Monitoring Assisted Reproductive Technology documents that more than 460,000 IVF procedures were performed in the year 2000 in more than 49 countries (Adamson et al., 2006), which is a 10% increase in the brief two year period of 1998 – 2000.

Studies have suggested an association between IVF and adverse perinatal outcomes that may affect the mother's health and the health of her newborn. It has been difficult to determine if these associations are due to the IVF procedures themselves or other factors related to the diagnosis of infertility. Since uncertainty remains regarding this association, further research is required to determine the health of the mother, her pregnancy, and her newborn, and to identify other factors that may predict adverse outcomes.

Statement of the Problem

Research studies show that there may be an association between treatment for infertility and adverse perinatal outcomes such as low birthweight (LBW) defined as a birthweight less than 2500 grams, and preterm delivery (PTD) defined as a delivery before 37 weeks gestation. This is of great concern because LBW and prematurity are determinates of neonatal morbidity and mortality (Chung et al., 2006). LBW is associated with neurological problems such as cerebral palsy (O'Shea, Klinepeter, & Dillard, 1998), cognitive and neuromotor difficulties (Lems, Hopkins, & Samson, 1993), and behavioral problems during childhood (Buck, Msall, Schisterman, Lyon, & Rogers, 2000; Hille et al., 2001; Saigal, 2000; Saigal, Rosenbaum, Szatmari, & Campbell, 1991; Saigal, Szatmari, Rosenbaum, Campbell, & King, 1991). LBW and PTD infants also

have been identified as having difficult temperaments (Weiss, Jonn-Seed, & Wilson, 2004). A cohort study that followed 1,338 preterm children (gestational age < 32 weeks) who were born in 1983 found that 40% were not able to fully function as independent adults (Walther, den Ouden, & Verloove-Vanhorick, 2000).

The use IVF, has increased dramatically worldwide since the birth of the first IVF-conceived child in 1978 (Adamson et al., 2006; Steptoe & Edwards, 1978). Of the studies that have been conducted to describe the outcomes of IVF pregnancies, some have suggested an association between IVF pregnancies and adverse perinatal outcomes. These pregnancies may be at increased risk for PTD and low birth weight LBW (ACOG Committee Opinion Number 324, 2005). Other treatments for infertility have been much less studied.

If an association between treatment assisted conception and PTD and LBW infants is clinically and statistically significant, women receiving treatment should be categorized as high risk, necessitating changes in the informed consent process and their obstetric care. The relationship between IVF, conventional treatments, and PTD and LBW infants must be fully investigated and factors that predict PTD and LBW in these pregnancies need to be identified so as to help prevent these complications and improve neonatal outcomes**.** The overall off goal of this study is to determine risk factors for PTD and LBW among women who have conceived a singleton pregnancy after a history of infertility. The specific aims are:

1. To identify the differences in health status, index pregnancy conditions, and perinatal outcomes (LBW and PTD) among three groups of women: fertile women who conceived a singleton pregnancy spontaneously, women who have a

history of infertility who conceived a singleton spontaneously, and women who have a history of infertility who conceived a singleton pregnancy with treatment.

2. To determine whether there is a relationship between fertility conception status and PTD or LBW when controlling for maternal age and nulliparity.

A review of the literature was conducted to identify factors that may influence the association between infertility, treatment and adverse perinatal outcomes. In order to address the question of perinatal outcomes after treatment for infertility, the Theory of Uncertainty in Illness is presented as a framework in which to examine the question and understand the experience. The chapter on the Theory of Uncertainty in Illness is followed by a chapter on the methods used to investigate the association between treatment for infertility and adverse perinatal outcomes. This is followed by the results of this investigation and a discussion of the implication of these findings.

CHAPTER 2 LITERATURE REVIEW

Studies indicate that there may be an association between IVF and adverse perinatal outcomes such as preterm delivery (PTD) and low birthweight (LBW). Few studies evaluate the outcomes of other treatments. The purpose of this chapter is to summarize the research on perinatal outcomes and review how infertility treatment may affect perinatal outcomes for mothers and their neonates.

Literature Review Methods

A search of the PubMed with MESH database between 1978 (the birth of the first IVF baby) and 2008 was conducted. The key words included ART, infertility, IVF, reproductive technology, infertility treatment, intrauterine insemination, ovulation induction, obstetric, perinatal, outcomes, low birthweight, LBW, small for gestational age (SGA), premature, preterm and PTD. The references of all studies and review articles also were reviewed for other relevant articles.

The Association Between IVF and Adverse Outcomes

Early observational studies conducted in Australia and Great Britain were the first to suggest a possible increase in adverse outcomes associated with IVF. (Australian In Vitro Fertilisation Collaborative Group, 1985; MRC Working Party on Children Conceived by In Vitro Fertilisation, 1990). Researchers in Australia found that 244 pregnancies resulted from IVF between 1980 and 1983, of which 135 (55%) were viable pregnancies. Of the 138 pregnancies that lasted at least 20 weeks, 30 resulted in a multiple birth (22.4%) as compared with approximately 1% in the Australian general

population. In single IVF pregnancies, 19% of the infants were PTD as compared with 6.2% in the Australian population. The researchers concluded that high rates of adverse perinatal outcomes for IVF pregnancies could be accounted for, in part, by risk factors such as maternal age and multiple pregnancy.

Researchers in Great Britain described the birth characteristics of children conceived by ART before 1988 and compared them with national perinatal statistics (MRC Working Party on Children Conceived by In Vitro Fertilisation, 1990). Of the 1,267 pregnancies achieved by IVF, 1,581 live born and stillborn children resulted. Additionally, 24% (278) were preterm compared with a 6% national average, and 32% (406) of 1,269 babies weighed less than 2,500 g compared with 7% of national births. The British researchers concluded that the high percentage of LBW and preterm babies for IVF pregnancies was largely, but not entirely, due to the high frequency of multiple births.

Subsequent to the first studies, researchers in other countries began reporting results from national IVF registries in Israel, Finland, France, and Sweden (Bergh, Ericson, Hillensjo, Nygren, & Wennerholm, 1999; French In Vitro National, 1995; Friedler, Mashiach, & Laufer, 1992; Gissler, Malin Silverio, & Hemminki, 1995). The objective of these studies was to describe the characteristics of pregnancies, deliveries, and infants conceived by IVF.

Israeli researchers surveyed births between 1982 and 1989 in all public hospitals (Friedler et al., 1992). They found that the 1,149 deliveries of children conceived by IVF resulted in 1,475 infants (98% were the result of conventional IVF). Multiple births occurred in 23.6% of the ART deliveries. LBW newborns were significantly higher in

the IVF multiple births and occurred in 28.6% of all deliveries. Perinatal mortalities occurred at double the rate of the national average (22.8/1,000). The incidence of major congenital malformations was 2.2%, which was not higher than in the general population.

French researchers reported data from 7,024 IVF pregnancies that resulted in 5,371 deliveries and 6,879 infants (French In Vitro National, 1995). More than a quarter (26.8%) of the IVF deliveries were multiple births, almost a third (29.3%) of the births were preterm, and more than a third (36.2%) of the infants were LBW. Perinatal and neonatal mortality rates were higher than the national average. The researchers concluded that the main determinate of adverse outcomes was multiple birth pregnancies; however, prematurity also was more prevalent among IVF singleton newborns.

Finnish researchers linked data from national IVF registries to the national Medical Birth Register for 1991 to 1993 (Gissler et al., 1995). IVF-assisted births accounted for 1,015 of the 191,712 pregnancies in Finland during that period. Multiple births accounted for 25% of the IVF deliveries compared with 1.1% in the general population, and 25% of the newborns weighed less than 2,500 g (LBW) compared with 5% in the general population. This study identified differences between the IVF and fertile study groups; the IVF mothers were older, more often married, more educated, smoked less, and had fewer previous pregnancies and births than the fertile group. The researchers adjusted for the mothers' demographic information when calculating odds ratios (OR). This study's major strength is that it examined entire cohorts of IVF births and all births in Finland, as opposed to taking a sample from each population.

Swedish researchers collected data from all IVF clinics in Sweden and compared the obstetric outcomes of babies (N = 5,856) born between 1982 and 1995 with all babies

born in the general population (N = 1,505,724) during the same period (Bergh et al., 1999). The data were stratified for maternal age, parity, previous infertility, year of birth, and multiple gestation pregnancy. The researchers found that multiple births occurred in 27% of IVF pregnancies compared with 1% in the comparison group. More IVF babies were born preterm (< 37 weeks, 30.3% vs. 6.3% for the comparison group), and more IVF babies were LBW (< 2,500 g, 27.4% vs. 4.6% for the comparison group). The perinatal mortality rate was 1.9% in the IVF group and 1.1% in the comparison group. The researchers concluded that the high frequency of multiple births and maternal characteristics were the main factors that led to adverse outcomes, not the IVF technique.

To summarize, studies of national IVF registries indicated that there might be an association between IVF and adverse perinatal outcomes. They reported increased rates of, PTD, and LBW infants compared with expected rates in the general population. However, they compared national birth statistics with pregnancies achieved by ART and therefore were limited by the absence of matched controls and lack of an adequate appropriate comparison group. This descriptive study design also is unable to identify possible predictors for the adverse perinatal outcomes. Although many of the studies analyzed large study populations (more than 1,000 births), other studies had small sample sizes that limited the generalizability of their results.

Perinatal Outcomes of Treatment Assisted Multiple-Gestation Pregnancies

One of the most significant complications associated with infertility treatment is the high frequency of multiple-birth pregnancies and associated poor perinatal outcomes (Keirse & Helmerhorst, 1995). The etiology of these perinatal outcomes, however,

remains uncertain, although the already high-risk nature of multiple-gestation pregnancies may be related to confounders such as ART treatment, maternal age, and parity (Helmerhorst, Perquin, Donker, & Keirse, 2004). Few studies have considered whether multiple-gestation pregnancies conceived through IVF demonstrate similar increased risks of PTD, LBW, and PM compared with naturally conceived multiple birth pregnancies and their results are inconsistent. Of the observational studies discussed earlier, Finnish researchers compared 269 IVF multiple-gestation births to 2,316 naturally conceived multiple-gestations and found a significant increase in PTD (OR = 2.41, CI: 1.98, 3.20), LBW (OR = 1.89, CI: 1.55, 2.29), CS rate (OR = 1.36, CI: 1.10, 1.69) and newborn length of stay ≥ 1 week (OR = 1.51, CI: 1.27, 1.78) (Gissler et al., 1995). No difference in perinatal mortality between the two groups was observed. On the other hand, using national data, American researchers found that twins conceived with ART demonstrated risks of term and preterm LBW that were similar to those in the general population of twins (OR = 1.0, CI: 1.0, 1.1) (Schieve et al., 2002). Another group of American researchers analyzed data from 424 ART twin pregnancies and 2,143 spontaneous twin conceptions and found no significant associations between ART and preterm labor, LBW, VLBW, or fetal growth restriction (Luke et al., 2004).

Case-control studies report conflicting results as well. Israeli researchers showed that patients who conceived with the assistance of IVF had a significantly higher risk for CS delivery (OR = 2.17, CI: 1.74, 2.70) and a lower mean gestational age at birth (34.62 weeks vs. 35.95 weeks, $p < .001$) compared with their controls (Adler-Levy, Lunenfeld, & Levy, 2007). Belgian researchers who compared 1,241 ART twin pregnancies with 1,241 spontaneously conceived twin pregnancies, matched for age and parity, observed

no significant differences in birthweight, incidence of perinatal mortality or morbidity, or congenital malformations but found an increased rate of CS delivery in the ART pregnancies (OR = 1.41, CI: 1.19, 1.66) (Dhont, De Sutter, Ruyssinck, Martens, & Bekaert, 1999). Two studies with small sample sizes (*n* = 103) (Koivurova et al., 2002) and (*n* = 96) (Koudstaal, Bruinse et al., 2000) failed to show significant differences in PTD rates.

A recent study conducted in the U.S. (Boulet et al., 2008) selected twin deliveries with and without indication of ART from Massachusetts live birth and infant death records from 1997 to 2000 and linked them to the US ART surveillance system. The sample was restricted to deliveries by mothers with high socioeconomic status, private health insurance, and intermediate/plus prenatal care use. The final study sample included 1,446 ART and 2,729 non-ART twin deliveries. ART twins were less likely than non-ART twin deliveries to be very preterm (OR = 0.75, CI: 0.58, 0.97) or include a very low birthweight infant (OR 0.75, CI: 0.58, 0.95) or infant death (OR = 0.55: 0.35, 0.88), controlling for maternal age, race, ethnicity, education, smoking, prenatal care and hospital care level. In stratified analyses, these findings were maintained for primaparous women, but there was no risk difference among multiparous ART and non-ART twin deliveries.

The risk of multiple gestation births due to IVF can be managed by limiting the number of embryos transferred (ACOG Committee Opinion Number 324, 2005). The American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology have developed recommendations for the number of embryos to be transferred to reduce the risk of multiple gestation births (Practice Committee of the

American Society for Reproductive Medicine, 2006). Two studies suggest that the overall rate of PTD and LBW has declined because the number of embryos transferred to the uterus has been reduced over time and ART-conceived pregnancies receive increased perinatal monitoring (Klemetti, Gissler, & Hemminki, 2002; Schieve, Rasmussen et al., 2004). In Finland, the IVF multiple-birth rate declined from 27% in the first study period of 1991-1993 to 21% in the second study period of 1998-1999. Additionally, in singleton pregnancies, the OR for PTD decreased from 2.2 (CI: 1.8, 2.8) to 1.8 (CI: 1.5, 2.1), and the OR for LBW decreased from 2.4 (CI: 2.0, 2.9) to 1.7 (CI: 1.4, 2.1), while in multiple-birth pregnancies, the PTD OR decreased from 2.4 (CI: 2.0, 2.9) to 1.5 (CI: 1.2, 1.7) and LBW decreased from 1.9 (CI: 1.6, 2.3) to 1.1 (CI: 1.0, 1.3) (Klemetti et al., 2002). In the U.S., the percent of term LBW infants declined 64% from 1996 to 2000, while preterm LBW rates remained stable (Schieve, Rasmussen et al., 2004). Data collected on 62,551 infants born as a result of ART during this period documented that the absolute risk for term LBW among ART singletons had declined by 64% by the year 2000.

Perinatal Outcomes of Treatment Assisted Singleton Pregnancies

Once early population-based studies identified multiple-gestation pregnancies as a major risk factor for adverse perinatal outcomes in ART-conceived pregnancies, researchers began to study perinatal outcomes of ART singleton pregnancies to determine if they too carried an increased risk of adverse perinatal outcomes. A 1994 study conducted in Britain compared the outcomes of IVF and naturally conceived pregnancies and found a 14% rate of PTD (RR = 1.8, CI: 1.3, 2.4), a 14% rate of LBW (RR = 1.8, CI: 1.3, 2.4), and an 18% rate of SGA (Tan et al., 1992). No differences were found in the

rates of stillbirth, perinatal mortality, or congenital malformations. A subsequent study, conducted in Australia, found that the overall frequencies of SGA and very small for gestational age (VSGA) in the ART population were higher than in the comparison group of spontaneous conceptions from the same geographical region. Results included a 4.7% rate of VSGA compared with 3% in the spontaneous conception group (OR = 1.6, CI: 1.05, 2.46), a SGA rate of 16.3% compared with 10% rate in the spontaneous conception group (OR = 1.8, CI: 1.4, 2.2), and 16% PTD rate compared with 6.2% ($p < .001$) for the spontaneous conception group (Wang et al., 1994).

American researchers used population-based data to compare the rates of LBW (≤ 2,500 g) and very low birthweight (VLBW; ≤ 1,500 g) among infants conceived with ART with the rates in the general population (Schieve et al., 2002). Each year the Society for Assisted Reproductive Technology (SART) collects data from roughly 95% of the ART clinics in the U.S. and provides these data to the Centers for Disease Control and Prevention. The researchers studied 42,463 IVF infants born in 1996 and 1997 and used as a comparison group all 3,389,098 infants born in the U.S. in 1997. Of singleton infants born at 37 weeks gestation or later, those conceived with ART had a LBW risk that was 2.6 times that in the general population (CI: 2.4, 2.7).

To estimate whether singleton pregnancies are at higher risk of perinatal mortality, PTD, SGA, and LBW or VLBW, researchers at the University of California, San Francisco conducted a meta-analysis of 15 studies comprising 12,283 IVF and 1.9 million spontaneously conceived singletons (Jackson, Gibson, Wu, & Croughan, 2004). Compared with spontaneous conceptions, IVF singleton pregnancies were associated with significantly higher odds of PTD (OR = 2.0, CI: 1.7, 2.2), LBW (OR = 1.8, CI: 1.4,

2.2), VLBW (OR = 2.7, CI: 2.3, 3.1) and perinatal mortality (OR = 2.2, CI: 1.6, 3.0). The researchers concluded that women considering IVF should be advised of the increased risk for adverse perinatal outcomes and that obstetricians should manage IVF-concieved pregnancies as high risk.

A recent population-based cohort study (Romundstad et al., 2008) was conducted in Norway to assess the effects of technology and maternal factors on perinatal outcomes after ART. Investigators compared pregnancy outcomes in women who had singleton pregnancies conceived both spontaneously and after ART. ART conceptions were associated with lower mean birthweight (difference 25 g, CI: 14, 35), shorter duration of gestation (-2 days, CI: 1.6, 2.3), and increased risks for SGA (OR = 1.26, CI: 1.1, 1.44) and perinatal death (OR = 1.31, CI: 1.05 to 1.65) as compared to spontaneous conceptions. In the sibling relationship comparison group there was no difference in gestational age or birthweight leading researchers to conclude that the differences in adverse outcomes of ART compared with those in the general population could be attributable to the factors leading to infertility, rather than to factors related to the reproductive technology.

Case-Control Studies of Singleton ART Pregnancies

Although some of the early singleton studies used population-based estimates for comparative purposes, other studies used a case-control design to strengthen the validity of their findings. A case-control study compares people who have a disease or condition with others who do not. In this case, the disease or condition would be infertility and the comparison would be between women who conceived through IVF and women without a

history of infertility who conceived spontaneously. The comparison group allows researchers to determine if the prevalence of adverse perinatal outcomes is greater in the infertility treatment group than in the spontaneous conception group (Gordis, 2004). Those who conduct case-control studies are always concerned that cases and controls often differ in other characteristics than the one under study. To minimize this disparity, researchers can select controls so that their characteristics are as similar to the cases as possible (Gordis, 2004). As noted, patients undergoing IVF are often older and more frequently primiparous (pregnant for the first time). Thus, case-control studies that evaluate risks associated with increased singleton pregnancies should match cases and controls on maternal age and parity, or they should control for these differences in the analsyes. Therefore studies which did not match on age or parity (Isaksson, Gissler, & Tiitinen, 2002; Tallo et al., 1995; Tough, Greene, Svenson, & Belik, 2000) will not be reviewed in this section.

To determine if singleton IVF pregnancies have a higher risk of perinatal complications than naturally conceived pregnancies, Belgian researchers investigated 140 singleton IVF pregnancies and 140 matched control pregnancies composed of women without a history of infertility and was matched on parity, maternal age, height and weight, and a singleton pregnancy of more than 20 weeks gestation that ended at the same time as the case being considered. They found that 16 IVF pregnancies and 2 control pregnancies ended preterm, resulting in the birth of neonates with lower birthweight in the IVF group ($p < .01$) (Verlaenen, Cammu, Derde, & Amy, 1995). Placenta previa occurred four times in the IVF group but did not occur in the control group. Delivery by elective CS for obstetric reasons was performed 10 times in the IVF

group but was not performed in the control group ($p < .01$). There also were eight minor congenital malformations in the IVF group but none in the control group ($p < .01$). The researchers concluded that singleton IVF pregnancies carry a greater antenatal risk than matched controls.

In contrast, another study designed to determine if singleton IVF pregnancies pose an increased risk of adverse perinatal outcomes than naturally conceived pregnancies, was conducted by Israeli researchers who analyzed data from 260 singleton IVF pregnancies and 260 naturally conceived controls matched for maternal age, parity, ethnic origin, and location and date of delivery (Reubinoff et al., 1997). A power analysis was not reported. The researchers found that the rates of preterm labor, LBW, SGA, VSGA, NICU admission, and perinatal mortality were comparable in both groups and concluded that singleton IVF pregnancies do not pose an increased risk for prematurity, LBW, or maternal or fetal complications.

In the Netherlands, researchers used an elaborate matching process to assess whether IVF pregnancies carry an increased risk of adverse outcomes (Koudstaal, Braat et al., 2000). Three hundred seven IVF pregnancies were compared with 307 control pregnancies based on the same hospital for obstetric care, maternal age, parity, ethnic origin, date of parturition, height and weight, and smoking history. In cases with spontaneous onset of labor, gestational age at delivery was 3 days shorter in the IVF group (275 vs. 278 days, $p = .05$) than in the control group and although this difference was not significant, it might explain why the proportion of SGA neonates was higher in the IVF group (16.2 vs. 7.9%, $p < .001$) than in the control group. The researchers

concluded that the combined results denote a difference in outcomes between IVF and control pregnancies.

A recent study was designed to evaluate perinatal outcomes in IVF with intracytoplasmic sperm injection (ICSI) conceived singleton pregnancies in the Netherlands (Knoester et al., 2008). The study population included 87 children conceived by ICSI, 92 matched IVF conceived children and 87 naturally conceived children from singleton pregnancies born between June 1996 and December 1999. Information on pregnancy and the perinatal period was obtained from questionnaires. Risk of PTD was greater after ICSI (p = .014) than natural conception, however, there was no difference between the groups for LBW. At the time of pregnancy, the age of ICSI parents was higher than the age of parents with natural conceptions, with a mean difference for maternal age of 2.3 years.

A case-control study with a large sample size including all pregnancies conceived with the assistance of ART in the Dutch-speaking part of Belgium from 1992 to 1997 found significant differences in three perinatal outcomes (Dhont et al., 1999). Singleton pregnancies (N = 3,057) were matched for maternal age, parity, fetal sex, plurality, and date of delivery with pregnancies from a regional registry. The outcomes that were significantly increased in IVF conceptions included perinatal mortality for singletons (OR = 2.6; CI: 1.4, 4.8), birth before 33 weeks of gestation for singletons (OR= 3.5, CI: 2.2, 5.7), and delivery by CS (OR = 1.7, CI: 1.5, 1.9). The researchers concluded that perinatal outcomes of singleton pregnancies conceived with IVF are significantly worse than those of spontaneously conceived singleton pregnancies because of the increased rate of preterm birth.

Other Perinatal Complications

Although most studies have examined PTD and LBW in IVF pregnancies, the increased incidence of other perinatal complications also has been reported. Placenta previa has been reported in women who conceived singleton pregnancies with ART (Schieve et al., 2007; Tan et al., 1992; Tanbo, Dale, Lunde, Moe, & Abyholm, 1995; Verlaenen et al., 1995). A meta-analysis of six small studies reported a three-fold higher risk associated with ART treatment (Jackson et al., 2004), and investigators in Norway found a six-fold higher risk of placenta previa in singleton pregnancies conceived by ART compared with naturally conceived pregnancies (OR = 5.6, CI: 4.4, 7.0) (Romundstad et al., 2006). Placenta previa also occurred more frequently in IVF mixed-sex twins even after adjusting for maternal age and parity (Smithers et al., 2003). It remains uncertain if the increased risk of placenta previa is caused by factors related to ART or associated with other maternal factors.

Rates of CS have been reported to be higher in most singleton and twin IVF studies (Adler-Levy et al., 2007; Dhont et al., 1999; Tanbo et al., 1995; Verlaenen et al., 1995) but not all (Lambalk & van Hooff, 2001). This finding may reflect confounding variables associated with elective and emergent CS, such as patient preference or heightened anxiety over much desired pregnancies. The literature also reports the increased incidence of other perinatal complications including: placental abruption (Perri et al., 2001; Shevell et al., 2005); antepartum uterine bleeding (Daniel et al., 2000; Smithers et al., 2003); gestational diabetes (Adler-Levy et al., 2007; Jackson et al., 2004; Maman, Lunenfeld, Levy, Vardi, & Potashnik, 1998); and pregnancy-induced

hypertension (Daniel et al., 2000; Jackson et al., 2004; Maman et al., 1998; Shevell et al., 2005; Tallo et al., 1995; Tanbo et al., 1995).

Factors Influencing Adverse Perinatal Outcomes

Women with a history of infertility may be at risk for antenatal health complications that may affect the pregnancy's outcome. A population-based study of 3,316 ART-conceived births compared with 157,066 naturally conceived births found that American women who conceived with ART were more likely to enter pregnancy with pre-existing diabetes (RR = 2.2, CI: 1.02, 4.9; Schieve et al., 2007). Adverse outcomes also have been attributed to the underlying infertility, but whether particular etiologies of infertility pose greater risk than others remains uncertain (Chung et al., 2006; Isaksson et al., 2002; Kovalevsky, Rinaudo, & Coutifaris, 2003; Schieve, Ferre et al., 2004). Preconceptual events, such as exposure to hormonal medications used during IVF, and the manipulation of gametes and embryos in the laboratory, also have been suggested as possible causes (Chung et al., 2006; Hansen, Kurinczuk, Bower, & Webb, 2002; Johnson et al., 1995). A case-control study to determine the effect of components of IVF treatment and the etiology of infertility on perinatal outcomes examined 435 pregnancies and found no effect of infertility etiology, dose or type of medication used for ovarian stimulation, or use of embryo-manipulation techniques on perinatal outcomes (Chung et al., 2006). After adjusting for multiple births, the researchers found that ovarian hyper-stimulation syndrome and suboptimal embryo development were associated with adverse outcomes in pregnancies achieved through IVF.

Australian researchers evaluated the effects of low and high technology treatment of infertility as compared to spontaneously conceived pregnancies on pregnancy outcomes and found an increased incidence of preterm birth with increasing levels of treatment (Wang, Norman, & Kristiansson, 2002). Low technology treatment consisted of intrauterine insemination (IUI) with minimal gonadotropin stimulation. High technology treatment consisted of ART procedures defined as IVF and gamete intra-fallopian tube transfer (GIFT) procedures. To eliminate the confounding effects of multiple births on PTD and LBW, only singleton pregnancies were evaluated for this study. Researchers found that woman who received high technology treatment were older (p = .01). Compared with the controls, the low technology treatment group had an approximately 50% added risk of preterm delivery and the high technology treatment group had more than twice the risk of preterm birth. This study was the first to compare both low technology and high technology assisted births to spontaneous conceptions in the general population; however, it is not clear whether women with a history of infertility who later conceived spontaneously were excluded from the comparison group.

An Israeli study also investigated the influence of level of treatment on perinatal outcomes (Maman et al., 1998) by comparing obstetric outcomes of twin pregnancies conceived by IVF, ovulation induction, with spontaneous conceptions. Controlling for maternal age and nulliparity, the researchers demonstrated that twin pregnancies conceived with the assistance of IVF had a significantly lower gestational age at birth (OR = 0.91, CI 0.88, 0.94).

Swedish researchers attempted to elucidate infertility in relation to risk factors and perinatal outcomes considering treatment-related and treatment independent

pregnancies (Sundstrom, Ildgruben, & Hogberg, 1997). Treatment related pregnancies consisted of all treatments offered at a university-based clinic including: IUI, ovulation induction medication, surgery to correct tubo-pelvic disorders, and IVF. When comparing 131 treatment independent pregnancies to 135 singleton treatment-related pregnancies, the mean age of the mothers did not differ; however there was an increased risk of PTD and LBW in the treatment related group ($p < .05$).

Critique of the Literature on Perinatal Outcomes

An accumulating body of research suggests that infertility treatment may be associated with adverse perinatal outcomes (Buck Louis, Schisterman, Dukic, & Schieve, 2005). Early reports from several countries signaled the first indication that rates of adverse perinatal outcomes may be elevated in IVF-conceived pregnancies. These studies used descriptive (cross-sectional and case series) and retrospective (case-control) designs, and many used population based estimates for comparison. These techniques are often subject to surveillance bias and difficulties associated with the selection of control groups (Barlow, 2002). Women who conceive through IVF are often older and more often pregnant for the first time than those in the general population, thus these maternal characteristics might influence pregnancy outcomes. Other factors that may influence outcomes include: the etiology of infertility, increased multiple pregnancy rates, exposure to fertility drugs, and the effects of the fertility treatment (Barlow, 2002). These potential factors make it difficult to separate possible treatment effects from the underlying fertility impairment (Buck Louis et al., 2005). Therefore we need comprehensive studies that include comparisons between infertile women who undergo treatment to conceive a

singleton pregnancy, women with a history of infertility who then conceive a singleton pregnancy spontaneously, and fertile women with no history of infertility who conceive a singleton pregnancy spontaneously.

Other methodological problems for many perinatal outcome studies is the lack of statistical power or the use of small sample size (Howe, Sayegh, Durinzi, & Tureck, 1990; Koudstaal, Bruinse et al., 2000; Tanbo et al., 1995; Verlaenen et al., 1995; Westergaard, Johansen, Erb, & Andersen, 1999) and/or the lack of confounding variables. In addition, low response rates, missing data, and subjects lost to follow-up are common problems in longitudinal studies. The study designs also have a potential for treatment or selection bias because only one of the study designs included blinded investigators and all obstetricians knew which of their patients had ART-assisted conceptions.

Most studies still report simple statistical methods, such as *t*-tests and chi-square tests, and do not account for the multiple confounders and the lack of independence in pregnancy outcomes. ART observations, which are generally not independent, include multiple oocytes, multiple embryos, multiple gestations, and multiple treatment cycles. Clustering is a form of dependency that commonly occurs in ART data on several levels, including within menstrual or treatment cycles within each woman (Buck Louis et al., 2005). Because most studies were conducted in Australia, Europe, and Israel, they lack generalizability to the U.S. due to significant differences in treatment availability and populations. Studies conducted with American populations are limited in number (Boulet et al., 2008; Chung et al., 2006; Howe et al., 1990; Luke et al., 2004; Schieve et al., 2007; Schieve, Ferre et al., 2004; Schieve et al., 2002).

While most studies compared ART pregnancies to the general population, several studies did compare the effects of various types of infertility treatment on the risk of adverse perinatal outcomes. One study compared ART with non-ART pregnancies in the same mother with pregnancies of a fertile control group (Romundstad et al., 2008) and found that although birth weight and gestational age did not differ between the ART and non-ART pregnancies within the same mother, their risk for adverse outcomes was greater when compared to fertile women, leading the researchers to conclude that factors leading to infertility were responsible for the increased risk of PTD and LBW. However, this study (Romundstad et al., 2008) lacked independence between the groups.

Finally, no common independent risk factors have been identified for adverse perinatal outcomes like PTD and LBW. Although recent studies are beginning to hypothesize etiologies for such outcomes (e.g, gestational diabetes or ART treatment), continued research is needed. The ideal design for studying the effects of treatment on perinatal outcomes is a randomized, controlled clinical trial (RCT); however, this would be ethically impossible because it would require administering treatment to fertile couples (Buck Louis et al., 2005). Thus, differentiating infertility treatment effects from underlying causes of infertility is difficult, but case-control and cohort studies are the strongest scientific designs available to study this phenomenon.

Summary

The principle findings of the foregoing review reveal that over 460,000 IVF procedures are being performed on women in more than 49 countries around the world annually to treat infertility, and IVF has been linked to several adverse perinatal events,

including PTD, LBW, multiple gestation, and increased rates of pre-eclampsia and CS delivery. Although most of the studies have found an association between ART and adverse perinatal outcomes, a few studies did not. The mostly commonly reported perinatal outcomes following IVF are PTD and LBW. In this review, six early population-based studies found an increased rate of PTD and LBW following IVF. In IVF conceived pregnancies, PTD rates ranged from 11.6% to 28.6% and LBW rates ranged from 14% to 32% while multiple birth rates ranged from 23.6% to 26.9%. Some of the adverse outcomes associated with IVF are attributed to this increased rate of multiple gestations. The American College of Obstetrics and Gynecology, the American Society for Reproductive Medicine, and the Institute of Medicine support efforts to lower the risk of multiple birth with IVF by recommending a decrease in the number of embryos transferred (ACOG Committee Opinion Number 324, 2005; Institute of Medicine Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007; Rebar & DeCherney, 2004).

Adverse perinatal outcomes have been associated with maternal characteristics that are common to women undergoing ART treatment for infertility such as advanced maternal age and nulliparity. Thus, it is difficult for researchers to compile an age- and parity-matched comparison group of pregnant older women who did not undergo infertility treatments to conceive. But, researchers conducted case-control studies to assess the effect of maternal age, nulliparity, and multiple-birth gestations on perinatal outcomes following IVF. For case-control studies that evaluated twin gestations, two found increased rates of PTD and LBW, but four did not. For the five case-control studies that evaluated singleton pregnancies, three found an increased rate of PTD and

LBW, although one study found no difference between the rates of PTD and LBW for IVF when compared with spontaneously conceived pregnancies. One case control study compared singleton births from ART and non-ART conceptions in the same women and did not find a difference between PTD and LBW.

All of the studies reviewed have methodological or design limitations that make it difficult to differentiate the effect of ART treatment from underlying etiology and characteristics of infertility. Most of the studies were retrospective (i.e., case-control) or descriptive (case series or cohort), some lacked sufficient statistical power to detect differences in perinatal outcomes, and none could address the potential additive or interactive effect of infertility and ART treatment on perinatal outcomes. Most of the studies were conducted in Northern Europe and Israel where universal health care is provided and the populations are mostly White. Because few of the studies were conducted with American participants and the health care system is different between countries, generalizability of the findings to the U.S. is limited. Future studies should include longitudinal or case control designs in the U.S. to increase our understanding of the relationship between IVF and perinatal outcomes and how other variables may influence the health of mothers and their neonates.

Although the studies in this review have their limitations, they also have some strengths. Several have large sample sizes, and two of the cohort studies used a complete population instead of a representative sample. Studies have been conducted in Australia, Europe, the Middle East, and North America, and collaborations have occurred between countries.

Many of the researchers who found a positive association between IVF and perinatal outcomes have recommended that patients be counseled regarding this potential risk. Several also have suggested that improved obstetrical care may decrease the risk to mothers and babies. Two recent studies have reported an interesting trend towards decreased rates of PTD and LBW infants after IVF. These finding may be the result of improved IVF techniques such as transferring fewer embryos, better selection of patients undergoing IVF, and better and more intensive prenatal care for IVF pregnancies.

If an association can be established between IVF and adverse perinatal outcomes, educating health care providers about this risk may improve outcomes. In summary, the association between IVF and perinatal outcomes and the potential etiology of these adverse events remains uncertain. Further research into the perinatal outcomes of assisted reproduction is greatly needed.

CHAPTER 3 THEORETICAL FRAMEWORK

The theoretical context for this study of adverse perinatal outcomes in women who have conceived a pregnancy after having had a history of infertility is the Theory of Uncertainty in Illness because it addresses *the* key experiences of infertile women and couples: wondering if a desired pregnancy will occur and if that pregnancy will produce a healthy child.

Giving birth to and parenting a child is a nearly universal human desire. The United Nations' Universal Declaration of Human Rights, Article 16, and the Human Rights Act, Article 12, as (cited in Boivin & Pennings, 2005) declare it to be a basic human right. Infertility is defined as the inability of a couple to achieve conception after one year of unprotected intercourse or the inability to carry a pregnancy to a live birth (Speroff & Fritz, 2005). Advanced reproductive technologies (ART), such as in vitro fertilization (IVF), have become the medical treatment of choice for infertility. These procedures, however, add a dimension of uncertainty to the construct of infertility. Nancy Adler eloquently describes this complex phenomenon in her forward to a book exploring research on stress and coping associated with infertility (Stanton & Dunkel-Schetter, 1991):

> The experience of infertility is potentially one of the most painful events of life to which people must adjust. It is a complex experience affecting the woman, the man, and the couple. It is fraught with uncertainty and can lead to alternating hope and despair. It brings people into contact with the leading edge of biomedical technology, where uncertainties abound. (p. ix)

As defined by Adler and others, infertility undermines the very essence of those who experience the condition. Although much has been written on the prevalence and significance of this phenomenon, scant research exists on the long-term physical, social, or psychological outcomes associated with infertility or its treatment (Allan & Finnerty, 2007). Specifically, no research has yet described the role that uncertainty plays in the infertility experience, and little research has described the long-term experiences of women and couples who become pregnant by IVF. This chapter will explore that gap, examining the experiences and perceptions associated with the uncertainties of infertility and its treatment with ART, including IVF.

The Phenomenon of Uncertainty

The phenomenon of uncertainty was first conceptualized by researchers who studied stress and coping (Lazarus & Folkman, 1984). Uncertainty has been couched in terms of choice, decision-making, probability, and risk and has been described in relation to ambiguity, inconsistency, lack of information, unfamiliarity, unpredictability, and vagueness (Neville, 2003). Uncertainty has been described as one of the most negative aspects of life (Parsons, 1980) and is perceived as a significant stressor for infertile couples (Domar, Broome, Zuttermeister, Seibel, & Friedman, 1992). It has also been characterized as a significant predictor of quality of life (Germino et al., 1998) and has been said to affect psychosocial adaptation and disease outcomes (McCormick, 2002). Managing uncertainty, therefore, is essential in successfully adapting to life stressors, such as illness (Neville, 2003), or to the complex experience of infertility, widely recognized as a significant stressor. For example, infertile women report that infertility

has been the worst crisis of their life, more devastating than divorce or even the loss of a parent (Mahlstedt, Macduff, & Bernstein, 1987). The experience is traumatic for couples as well, whose hopefulness at the beginning of each menstrual or treatment cycle too often ends in grief when pregnancy has not been achieved.

Like many other life stressors, infertility is not a discrete event but an unfolding process. The beginning of the process is frequently marked by the passing of a year attempting to conceive without success, and by entry into medical treatment. The infertility process often continues over a long period of time as individuals contend with the prospect of being unable to conceive. "Indeed, in most cases, it is the possibility rather than the reality of infertility that is at issue, because there is some degree of ambiguity about the outcome," (Dunkel-Schetter, 1991, p. 29).

In her conceptualization of uncertainty, Mishel (1997) was the first to link relationships with the experience of illness and to combine nursing research with other disciplines to create a theoretical model. Mishel based her theory on definitions of uncertainty from her earlier work, which include (a) the inability to determine the meaning of illness-related events or to assign definite values to objects and events, and (b) the inability to accurately predict outcomes (Mishel & Braden, 1988) or having no cognitive schema for the illness event (Mishel, 1988). A cognitive schema is a person's subjective interpretation of illness, treatment, or hospitalization. According to the theory, uncertainty in illness reflects a neutral cognitive state that is neither desired nor dreaded until the implications of the uncertainty are determined and can be appraised as a danger or an opportunity (Mishel, 1988). Coping strategies are used during this assessment of the uncertainty.

The Theory of Uncertainty in Illness

Nursing theories can be classified along a continuum, beginning with concrete practice theories and ending with abstract grand theories (Smith & Liehr, 2003). The theory of uncertainty in illness, considered a mid-range theory, falls between practice theories and grand theories on the continuum, and contains both measurable and abstract concepts to explain how people construct meaning for illness, treatment, and outcomes. Infertility, with its associated treatments and unpredictable outcomes, is a condition well-suited to the framework of the uncertainty in illness theory.

Two versions of the uncertainty theory have been developed. Mishel (1988) developed the original theory, inspired by her father, who was dying of colon cancer (Mishel & Clayton, 2003). She noticed that he focused on those aspects of his illness that he could control, thus creating some predictability for himself. His efforts to understand his illness clarified the significance of uncertainty for Mishel. She proceeded to develop her theory to address the uncertainty, or the inability to determine meaning, during the diagnosis and treatment of an acute illness and for illnesses with a negative prognosis. Later, Mishel (1990) reconceptualized the theory to address the experience of one living with a chronic illness or a treatable illness that might recur. Because the reconceptualized theory of uncertainty in illness focuses on chronic health conditions, it is less relevant to infertility and will not be discussed in this paper.

Concepts of the Theory of Uncertainty

According to Meleis (2007), a theory's functional components refer to the relationships between its concepts (see Figure 1). The major concepts within the uncertainty theory include (a) *antecedents of uncertainty*, (b) *appraisal of uncertainty,* (c) *coping with uncertainty in illness*, and (d*) adaptation.*

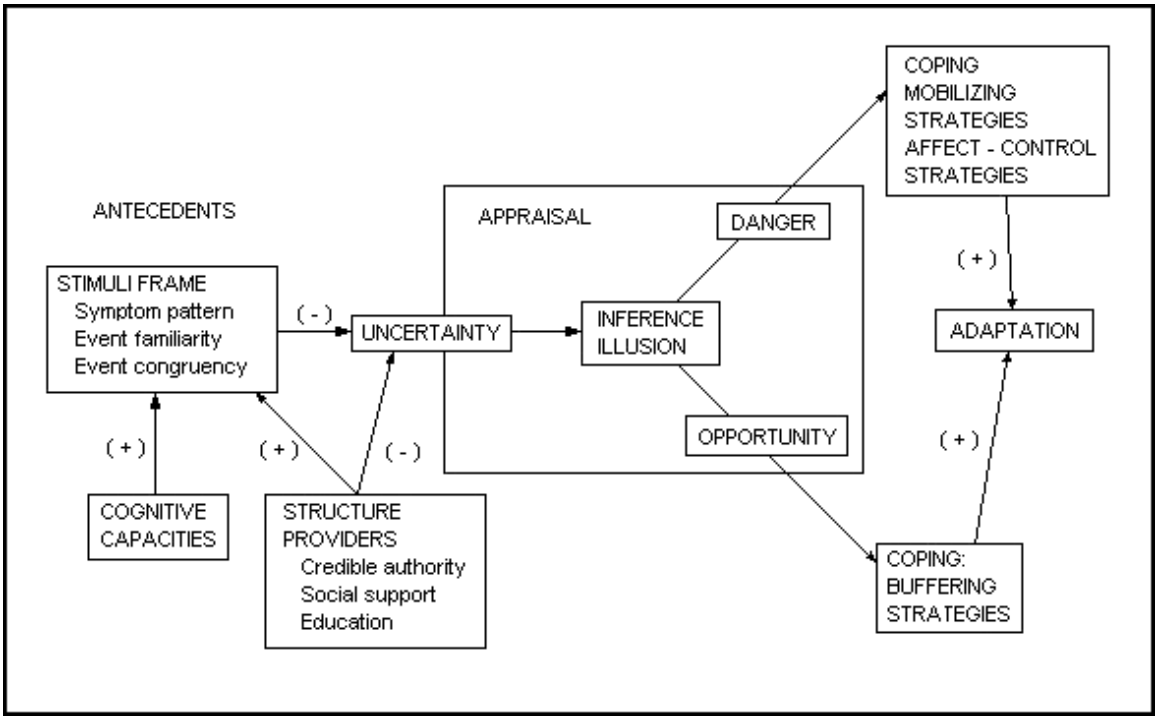

Figure 1. *Model of uncertainty in illness adapted from Mishel (1988).*

Antecedents of uncertainty. The most complex of the four components is the antecedents of uncertainty. According to Mishel (1988), the primary antecedents of uncertainty consist of information that is processed by the patient. The antecedents that may influence uncertainty include (a) *stimuli frame*, (b) *cognitive capacity*, and (c) *structure providers*.

The stimuli frame itself has three components: *symptom pattern, event familiarity,* and *event congruence*. These components provide the information that is processed by a

person to create a cognitive schema, but the lack of any of one component leads to uncertainty. Symptom pattern refers to the recognition of recurring symptoms as having a pattern. Based on this pattern, a person can infer a meaning for the symptoms. Event familiarity refers to recurrent situations or situations that contain recognizable information. When events are recognizable, they become familiar and a meaning can be determined for them. The third component, event congruence, refers to the relationship between the expected and the experienced outcome in an illness-related event. Because consistency allows a person to interpret an event, or infer its meaning, the components of the stimuli frame (symptom pattern, event familiarity, and event congruence) help a person to create a cognitive schema and to reduce uncertainty. Simply stated, their absence increases uncertainty.

Cognitive capacity, another antecedent of uncertainty, refers to a person's information processing ability. When a person tries to process too much information, overload occurs, reducing the person's ability to perceive symptom patterns, event familiarity, and event congruence.

Structure providers, the resources that assist a person in interpreting the stimulus being experienced, represent the second variable that influences the stimuli frame and resulting uncertainty. Structure providers include education, social support, and credible authorities, such as health care providers. When patients can process stimuli and construct a cognitive schema for an illness event, such as infertility, uncertainty is reduced. When a cognitive schema cannot be formed, the result is uncertainty.

Appraisal of uncertainty. Appraisal of uncertainty is the second major concept of the uncertainty of illness theory. Uncertainty occurs when a person fails to develop a

cognitive schema. According to this theory (Mishel, 1988), when a person is uncertain about an illness such as infertility, one of three situations has occurred: the event was not recognized, the event was recognized but not classified, or the event was recognized but classified incorrectly. Note, however, that uncertainty is neither a desired nor a dreaded experience until it is appraised. Appraisal of uncertain situations involves two processes: *inference* and *illusion*. The first process refers to general beliefs about oneself and one's relationship with the world; these include a person's beliefs about his or her mastery, resourcefulness, and ability to handle challenging situations. To access these personal resources, a cognitive schema must be developed that corresponds with past learning about an event similar to that being experienced. The second process, illusion, refers to beliefs constructed out of uncertainty that are viewed with an emphasis on their positive aspects. Illusions may be seen as appropriate in situations where an individual is helpless to change an outcome. While illusions are sometimes likened to denial, they may also be seen as helpful in protecting people who are in the initial stages of a serious illness. Illusions are often fostered by family, friends and health care providers in an attempt to help a patient maintain hope. Illusions generated from uncertainty are appraised as an opportunity.

Coping with uncertainty in illness. The third major concept of the uncertainty theory is coping. Once an uncertain situation has been appraised as an opportunity or a danger, appropriate coping strategies can be developed and employed. When uncertainty is seen as a danger, coping strategies include *mobilizing* and *affect-management*. Mobilizing includes strategies of direct action, vigilance, and information seeking. Direct action includes changing health behaviors, such as losing weight or exercising more.

Direct action may also include seeking out social support. Little is written about vigilance with regard to uncertainty, however, it is believed to be most often used by the parents of sick children in the form of staying alert to changes in the child's condition, and to being directly involved in care and making decisions on treatments. Information seeking is the most widely used coping strategy and includes seeking information from significant others and health care providers. When mobilizing techniques fail to reduce uncertainty, affect-management techniques are then used, which include *blunting negative emotions*, *using wishful thinking*, and *redefining the uncertain situation*.

Uncertainty is seen as an opportunity or a preferable state when the alternative to the uncertainty is a negative outcome. The uncertainty allows a person to maintain hope and optimism. *Buffering* is a coping method that blocks new information that might change the perception of the uncertainty. It includes techniques such as avoidance, selective ignoring, and minimizing new information that could influence the perception of uncertainty as an opportunity.

Adaptation to uncertainty. Adaptation is the fourth major concept of the uncertainty theory. Whether uncertainty is seen as an opportunity or a danger, adaptation will occur when coping strategies have been effective. According to Mishel (1988), adaptation is defined as "bio-psycho-social behavior occurring within a person's individually defined range of usual behavior" (p. 231), which has been operationalized as health, life quality, psychosocial adjustment, recovery, or stress. Mishel considers adaptation to be a neutral state that allows a person to continue with goal-directed behaviors meaning that an individual's activation level is neither higher nor lower than their usual level or norm.

Assumptions of the Theory of Uncertainty

A theory's structural components are the underlying but consciously stated assumptions that lead to a set of propositions that are to be tested (Meleis, 2007). In the theory of uncertainty in illness, it is assumed that antecedents of uncertainty have an effect on the appraisal of uncertainty and that the appraisal of uncertainty, in turn, has an effect on the coping that influences adaptation to uncertainty. More specifically, uncertainty experienced as ambiguity and complexity is hypothesized as being influenced by antecedents from the stimuli frame and the structure providers. People use antecedents of the stimuli frame, symptom patterns and event familiarity, to reduce uncertainty. And, the stimuli frame is influenced by the antecedent variable of structure providers, those resources available to a patient to interpret the stimuli frame, which include education, social support, and credible authority (Mishel & Braden, 1988).

The theory identifies two mediating processes: *mastery* as a mediator of the relationship between uncertainty and appraisal, and *coping* as a mediator of the relationship between appraisal and emotional distress, which is one form of adaptation. (Mishel & Sorenson, 1991). While coping is presented as a major construct in the theory (see Figure 1), mastery's function is less well established. In relationship to the theory, mastery is described as the ability to influence negative events. When mastery is perceived to be high, a person will more likely experience uncertainty as an opportunity. When mastery is perceived to be low, then uncertainty is more likely to be perceived as a danger. However, mastery is not specifically linked to the concepts of illusion or inference, which also describe when uncertainty is seen as a danger or opportunity.

The uncertainty theory further assumes that coping mediates the relationship between appraisal and adjustment, which is another form of adaptation. Problem-focused forms of coping are hypothesized to be used in situations that are interpreted as manageable, and emotion-focused coping is believed to be used when a situation is interpreted as being unalterable. More specifically, uncertainty erodes a person's belief that he or she can manage a situation.

Applying the Uncertainty Theory to Infertility

This chapter will analyze how the uncertainty theory applies to women who are experiencing or have experienced infertility and ART treatment. Uncertainty in infertility may occur in several forms: ambiguity or lack of information concerning the diagnosis or cause of the infertility, complexity about its treatment and the system of care, and unpredictability of the course of the illness and prognosis for achieving a pregnancy. These forms well describe the experiences associated with infertility and treatment with IVF and will be discussed in relationship to the theory concepts.

Antecedents of Uncertainty Associated with Infertility

Stimuli frame. Stimuli frame refers to the form and structure of the stimuli that a person perceives. Many women and couples have no idea that they will have trouble conceiving until they attempt to do so for the first time. Many have conscientiously used contraceptives to avoid having an unplanned pregnancy. Often there are no symptoms associated with infertility, and patients are truly surprised when conception does not

occur easily. Diagnosing the causes of infertility is often difficult, and frequently women or couples are labeled as having *idiopathic* or *undiagnosed infertility*.

Cognitive capacity. Cognitive capacity is a person's ability to process information. For people without medical training, deciding how to proceed with infertility treatment is a difficult and uncertain task. Treatments are often complex, uncomfortable, and expensive, further stressing a couple that is contemplating how best to proceed in creating a family. More than 30% of ART births consist of twins, triplets, or even larger multiple births, and at least half of all ART neonates are products of a multiple conception (Reddy, Wapner, Rebar, & Tasca, 2007). Multiple births resulting from infertility treatments are a growing problem and can have a devastating effect on obstetric and pediatric outcomes and a family's quality of life (Balen & Rutherford, 2007). Less aggressive treatments may reduce this risk. Patients, however, are often reluctant to abandon aggressive treatments, such as medical ovulation stimulation and the implantation of large numbers of embryos into the uterus, because they promise higher rates of pregnancy. When implantation fails or there is a known genetic disorder, some couples consider preimplantation genetic testing. For couples thought to be at risk for having a child with a debilitating genetic disorder, IVF with preimplantation testing offers hope. However, abnormalities caused by the procedure cannot be ruled out, and pregnancy rates may be lower than undergoing IVF without preimplantation testing (ASRM, 2007).

Women and couples undergoing IVF often feel overwhelmed and inundated with information about their treatments and the attendant risks and benefits, adversely affecting their comprehension of the situation. Decisions about informed consent are

often made in a state of mental confusion. And patients often look to others for help when deciding how and when to proceed with treatment. Cognitive capacity is frequently diminished during the treatment phase of infertility care, which will affect the stimuli frame, according to the uncertainty in illness theory.

Structure providers. Structure providers are the resources that help a person to interpret the stimulus being experienced. Structure providers, such as nurses and physicians, play a major role in providing information that can help a person to develop a cognitive schema for the diagnosis of infertility. Patients need information about the causes of infertility, its treatments, and the risks and benefits associated with treatment. But, one appointment is rarely enough time for women and couples to understand the complete picture. A patient's cognitive capacity can be severely challenged by the volume and complexity of the information being presented. Diagnostic procedures are being scheduled, medications may be prescribed, treatment options and their risks and benefits are being reviewed, treatment success rates are being quoted, and patients are trying to comprehend the emotional and financial implications of their infertility. Clinics that treat infertility may direct patients to additional resources, such as reputable web sites, patient support groups, and clinic seminars for the community. Many clinics also provide psychological support to assist patients with the challenges yet to be faced in treating their infertility.

Although structure providers can be professional people, such as nurses or physicians, they can also be concepts, such as education, ethnicity, or socio-economic status, all of which play a part in accessing treatment for infertility. Racial, ethnic, and educational disparities exist in infertility status and treatment. Black and Hispanic

women experience infertility more often than White women, and women with a lower level of education experience infertility more often than those with a higher level of education (Bitler & Schmidt, 2006). And, Black women are more likely to endure infertility longer than White women before seeking treatment (Jain, 2006). Wide disparities exist in the quality and availability of infertility services in developed and developing nations (Nachtigall, 2006). All of these structure providers must be considered when evaluating the uncertainty of different women who experience infertility.

Appraisal of Uncertainty Associated with Infertility

Infertility is often perceived as a threat to one's ability to become a biological parent and to hold a valued place in one's family and society at large. However, infertility treatment is often seen as an opportunity to achieve that goal. As with any group of people who experience a health problem, infertile women and couples have varying degrees of cognitive capacity, but most need assistance to comprehend the information that medical and nursing staffs offer them.

According to the uncertainty in illness theory, the experience of uncertainty is neutral until it is appraised. The uncertainty associated with a diagnosis of infertility can be seen as an inference or an illusion. Inferences build upon a person's beliefs about one's ability and sense of mastery, while illusions build upon one's belief that an event has favorable aspects. Illusions have been linked to maladaptive adjustment, such as denial; however, illusions are also associated with beliefs that allow a person to confront a negative situation with hope (Mishel, 1988). For an infertile couple, illusions may

provide the hope that is needed to undergo treatments that have no guarantee of success. Those who pursue treatment may also rely on inferences about their sense of mastery of the complicated treatment that may be required to achieve a pregnancy.

Coping with Uncertainty Associated with Infertility

When uncertainty associated with infertility is seen as a danger, two coping strategies are common: mobilizing and affect-management. Mobilizing includes direct action, vigilance, and information seeking, which is the most widely used coping strategy associated with infertility and treatment. Patient support groups and web sites are often used even before the first medical appointment is scheduled. Friends and family may opine about which medical groups provide the best medical care. And, medical practices that provide infertility services routinely conduct free seminars for prospective patients, at which they answer questions about medical treatments, their costs and success rates, and the potential risks associated with treatment.

Even in women and couples who have not achieved a pregnancy, infertility can motivate them to mobilize meaning-based coping skills (Schmidt, Holstein, Christensen, & Boivin, 2005). Participants in a qualitative study (Daniluk, 2001) described how they learned to talk about existential aspects of life with their partners and how they learned to manage new and stressful situations. Affect-management techniques such as blunting negative emotions, using wishful thinking, and attempting to redefine the uncertain situation are often used during infertility treatment.

The uncertainty associated with infertility is seen as an opportunity or a preferable state when the alternative to the uncertainty is a negative outcome such as a failure to

ever become pregnant. The technique known as buffering might be employed. For example, many patients will continue to receive treatment even though the chance of a successful outcome is predicted to be quite low. Patients appear to be selectively ignoring or minimizing the likelihood that they may not become pregnant, effectively buffering themselves from a poor prognosis.

Once a woman becomes pregnant by IVF, her uncertainty does not disappear. In fact, it can increase. Current research indicates that singleton IVF pregnancies are associated with many adverse perinatal outcomes, including perinatal mortality, preterm delivery, low-birthweight babies, and small-for-gestational-age babies even after controlling for maternal age and parity (Jackson et al., 2004). Chromosomal abnormalities are slightly higher in ART babies, and well-documented malformations include cardiovascular defects, gastrointestinal defects, hypospadias and other genitourinary abnormalities, musculoskeletal defects, and neural tube defects (Reddy, Wapner, Rebar, & Tasca, 2007). Women and couples who are considering ART procedures should be counseled about the potential perinatal risks associated with IVF. Nurses should be mindful that when patients are advised of the increased risk to their unborn child, they face new uncertainties, including the potential for a complicated pregnancy and the arrival of an ill child.

Adaptation to Infertility

When women and couples fail to become pregnant, they must adjust to being unable to conceive a child. Many couples form a family in other ways, including adoption or collaboration with a third party in the conception of a child. This might mean

using an oocyte donor, a sperm donor, a host uterus as a gestational carrier, or a surrogate to provide both oocytes and the gestation of the pregnancy. Other women and couples choose to remain childless and find other ways to make their lives meaningful. Nurses can play a significant role in helping couples to adapt to their infertility by providing information about these other options. By providing this information early in the infertility treatment process, nurses allow couples to consider all of their options. Having a plan for infertility treatment, including all options to create a family, can reduce uncertainty for the woman or couple undergoing infertility treatment.

Critiquing the Theory of Uncertainty

Adoption by Researchers

The ultimate test of a theory is its adoption by others (Meleis, 2007). The theory of uncertainty has met that test, a fact amply demonstrated by the breadth of researchers who have used it. Researchers have used the uncertainty theory and its measurement scales to study acute and chronic illnesses and to explore many specific oncological conditions, such as breast cancer (Clayton, Mishel, & Belyea, 2006; Gil et al., 2006; Gil et al., 2005; Mishel et al., 2005; Porter et al., 2006), gynecologic cancers (Mishel & Sorenson, 1991), and prostate cancer (Bailey, Wallace, & Mishel, 2007; Bailey, Mishel, Belyea, Stewart, & Mohler, 2004; Mishel et al., 2002; Mishel et al., 2003). The theory has been adapted for use in both adults and children (Stewart, Lynn, & Mishel, 2005; Stewart & Mishel, 2000) and for different ethnic groups (Germino et al., 1998; Gil et al., 2006; Gill et al., 2004; Mishel et al., 2005; Porter et al., 2006). It has also been used to assess issues associated with quality of life (Padilla, Mishel, & Grant, 1992) and issues of

mastery and coping (Mishel & Braden, 1987; Mishel & Sorenson, 1991). Uncertainty theory has reportedly been used to investigate such varied illnesses as AIDS, arthritis, cardiac conditions, post-polio syndrome, and scoliosis (Neville, 2003). An entire book, *Uncertain Motherhood: Negotiating the Risks of the Childbearing Years* (Field & Marck, 1994), dedicated to qualitative nursing research, used Mishel's theory to study unexpected pregnancies, mothering a preterm baby or a child with a birth defect and the process of infertility treatment. This book contains the first research of uncertainty associated with infertility, but it does not address the uncertainty in illness theory model or suggest an alternative model for infertility research.

Testing the Theory

Before Mishel's work on uncertainty, there was no systematic measure of uncertainty as a variable with the potential to influence illness (Mishel, 1981). Only anecdotal descriptions of the concept were available. The *Mishel Uncertainty in Illness Scale* (MUIS), a 54-item instrument constructed with a 5-point Likert scale, was designed to capture the concept of uncertainty. The scale was developed after an exploratory study of hospitalized patients produced a list of statements on illness-related events. These statements informed the creation of four predictive subscales or factors: *ambiguity, lack of information, unpredictability,* and *lack of clarity*. The MUIS was subsequently developed and administered to hospitalized patients. The test results were subjected to classical factor analysis and an orthogonal rotation. Two-factor analyses were performed; items were reduced from 54 to 30 following the first analysis and from 30 to 2 on the second analysis. Factor 1 was labeled *multi-attributed ambiguity* with a

standardized alpha of .91, indicating a high degree of consistency with this factor. Factor 2 was labeled *unpredictability* and had a standardized alpha of .64, which shows only a modest level of consistency. Still, this study does suggest that ambiguity and unpredictability are the key ingredients of uncertainty.

Three validation studies confirmed that characteristics of an uncertain illness event are described by the theory and provide support for the MUIS's construct validity (Mishel, 1981). The first validation study was conducted "to test the proposition that patients undergoing rule-out diagnostic procedures perceive more uncertainty than medical and surgical patients with determined diagnoses," (pp. 261-262). Uncertainty scores from three patient groups (surgical group, $n = 68$, medical group, $n = 134$, and rule-out group, $n = 51$) were analyzed using a one-way analysis of variance. A significant group effect was found, $F(2,250) = 23.97$, $p < .001$. The rule-out group mean (87.62) on the MUIS was significantly greater than both the medical group mean (76.62) and the surgical group mean (65.64).

The second validation study tested the hypothesis that stress (as an indicator of adaptation) develops when coping methods fail. The MUIS and the Hospital Stress Events Scale were administered to 100 patients, and a Pearson product-moment correlation was used to assess the relationship between uncertainty and stress. The results indicated that uncertainty scores were correlated with hospital stress scores ($r = .35$, $p < .001$), supporting the theory's link between coping and adaptation. A multiple regression analysis investigating the relationship between the two uncertainty factors (multi-attributed ambiguity and unpredictability) and stress indicated that multi-attributed ambiguity accounted for 12% of the variability in the stress score. However, the

unpredictability factor did not add anything to the strength of the relationship. Therefore, "all of the variance in stress that could be accounted for by uncertainty was explained solely by the multi-attributed ambiguity factor," which appears to be a significant predictor of stress.

The third validation tested the hypothesis that uncertainty is related to a lack of comprehension or cognitive capacity. The MUIS and the comprehension interview were administered to 26 cancer patients on their first day of treatment. Results showed that a high level of uncertainty was correlated with a lower level of comprehension ($r = -.56$, $p < .002$), thus providing support for the assumption that cognitive capacity influences the appraisal of uncertainty.

Uncertainty theory can be extremely useful in nursing research. With the ability to measure uncertainty associated with illness, nurses can assess a patient's need for information or social support or assess a patient's adaptability to the uncertainties of living with a chronic illness. A quantitative correlational study (Mullins et al., 1995), designed to examine the role of uncertainty on adaptation by looking at psychological distress as an indicator for lack of adaptation found a positive correlation between levels of uncertainty and psychological distress when using the MUIS and the Symptom Checklist 90-Revised to evaluate 58 individual diagnosed with postpolio syndrome. With psychological distress serving as a marker for a lack of adaptation to an illness, this study supports the theory assumption that uncertainty has an effect on adaptation.

Increasingly, the MUIS is being used by nurses internationally. For example, a recent study of breast cancer survivors in Thailand (Wonghongkul, Dechaprom, Phumivichuvate, & Losawatkul, 2006) used both uncertainty as a theoretical framework

and the MUIS as a measurement to assess uncertainty, appraisal of coping, and quality of life. These nurse scientists found that seeking social support was the most commonly utilized coping strategy, and that it reduced stress among breast cancer survivors. The researchers concluded that uncertainty influences quality of life in breast cancer survivors and that coping strategies such as seeking social support could be used to promote adaptation to the condition of breast cancer. Based on such research, the phenomenon of uncertainty associated with illness is testable, and the MUIS appears to be a useful tool for testing the presence of uncertainty.

Three studies have evaluated different components of the theoretical model of uncertainty in illness. The first study (M. H. Mishel & Braden, 1988) tested variables associated with antecedents of uncertainty: symptom patterns and event familiarity that are a part of the stimuli frame, and education, social support, and credible authority that are part of structure providers. According to the theory, symptom pattern and event familiarity are inversely related to uncertainty. In the women receiving treatment for gynecological cancers, the effect of symptom patterns reduced the ambiguity perceived in the illness state, supporting the proposed relationship between symptom patterns and ambiguity as a type of uncertainty, when symptom pattern was considered independently of the structure provider variables. The participants appraised their illness more clearly when they could construct a pattern of their symptoms (Mishel & Braden, 1988). And, event familiarity significantly accounted for variance in the type of uncertainty associated with complexity perceived in treatment. The authors found that structure providers (social support and credible authority) had a direct influence on uncertainty, supporting the assumption that structure providers play a role in reducing uncertainty in illness.

The second study (Mishel & Sorenson, 1991) tested the appraisal and coping components of the uncertainty in illness model by evaluating the relationship between uncertainty and mastery in a sample of 131 women who were receiving treatment for gynecological cancer. Mastery, defined by the theorist as the ability to behave in a way that mitigates the aversiveness of an event (Mishel & Sorenson), was found to be a significant mediator of the relationship between uncertainty and the appraisal of opportunity and danger. Higher levels of uncertainty significantly reduced the level of mastery, which is a component of appraisal. While this study found support for the relationship between appraisal and adaptation, little support was found for coping strategies as mediators between appraisal and degree of emotional distress or adaptation.

The third study (Mishel et al., 1991) attempted to replicate Mishel and Sorenson's test (1991). In the study sample of 100 women who were undergoing treatment for gynecological cancer, regression analysis was used to test the mediating effects of mastery and coping. Uncertainty was found to be significantly associated with both the appraisal of danger and opportunity and a sense of mastery. Mastery in turn had a mediating effect on both danger and opportunity appraisal. These findings support the finding in the earlier test of the model (Mishel & Sorenson, 1991), which found support for the relationships between uncertainty and appraisal, and appraisal and adaptation. The relationship between coping and adaptation was not supported by this study.

Although these studies are a good start in testing the theory of uncertainty in illness, portions of the theory still remain untested, such as (a) the relationship between cognitive capacity and the stimuli frame, (b) the relationship between inference and illusion on danger and opportunity, and (c) most of the coping strategies. The

relationship between coping and adaptation was supported in a validation study of the MUIS, but the relationship has yet to be supported by additional research.

Relevance to Nursing Practice

In general, the theory of uncertainty in illness appears to be pragmatic and generates testable hypotheses, the results of which can be applied toward improving the quality of nursing care. Theoretical models are considered useful when they can be applied toward practice, research, education, or administration (Meleis, 2007). The theory of uncertainty has the potential to be a relevant, applicable way to educate nurses about the experience of illness and to provide a framework for organizing care. The theory, however, has been criticized for its lack of parsimony and excessive use of jargon.

The first component of the theory, antecedents of uncertainty, uses complicated names, such as stimuli frame and structure providers. Several readings of the theory may be needed to realize that these are complicated terms for describing the basic issues that may influence uncertainty or those things that help a person make sense of the uncertainty. And, the terms illusion and inference, used in the second stage of the theory known as *appraisal,* are also unnecessary and add little to the understanding of how a person ultimately defines the uncertain experience as a threat or an opportunity. While mastery is thought to mediate whether uncertainty is seen as a danger or an opportunity, there was no link made between mastery and illusion (which is seeing uncertainty as an opportunity) and inference (which is seeing uncertainty as a danger). Also, the idea that uncertainty is a neutral state until it is appraised is questionable and unlikely when applied to those who are experiencing infertility. For a person who desires to have

children, the inability to conceive is certainly considered a danger or a threat, and it is unlikely that many would consider infertility an opportunity, until much later in the final stage of the model identified as adaptation.

Two phases of the theory that are very consistent with the experience of infertility are coping and adaptation. These experiences have been studied in great detail (Boivin & Schmidt, 2005; Finamore, Seifer, Ananth, & Leiblum, 2007; Hjelmstedt, Widstrom, Wramsby, & Collins, 2004; Pasch, Dunkel-Schetter, & Christensen, 2002; Wirtberg, Moller, Hogstrom, Tronstad, & Lalos, 2007) and document the experiences of uncertainty and how women and couples cope and adapt to this experience.

In addition, the concept of antecedents and their relationship to uncertainty have great relevance for infertility. When caring for patients undergoing infertility treatment, nurses must remember that the patients are experiencing intense uncertainty. This situation creates a continuing need for nurses to provide structure in the form of patient education. Answering questions before they are asked on topics such as appointment schedules, medication regimes, surgical procedures, adoption, and third party reproduction provides information that can be used by patients to create their own cognitive schema. When patients construct a schema, their level of uncertainty will be reduced.

A Guide for Infertility Research

Infertility research has not really used the uncertainty model as a guide to date. In her qualitative study, Harris (in Field & Marck, 1994) explored the uncertainty associated with infertility in order to generate a theory that could explain the experience

of women undergoing treatment to become pregnant. Harris coined the term *pregnology*, a combination of pregnancy and technology, to convey the use of science to achieve a pregnancy, and the term *living under the microscope* to describe the scrutiny that women feel while undergoing an infertility workup.

Most research of the experience of infertility has compared the experiences of infertile women to a comparison group of fertile women using standardized psychological measures. The MUIS and its associated theory evaluate the phenomenon of infertility in a unique way and add a new dimension to our understanding of the infertility experience. A study exploring those variables would be a good place to start. And, asking people to describe when they feel most uncertain and what creates and intensifies uncertainty would also enrich nursing knowledge and allow for the development of interventions to reduce uncertainty and the distress it causes.

Conclusion

This review lays the foundation for understanding the multifaceted phenomenon of infertility and treatments. The inability to have children threatens the very essence of some peoples' being. It can be frightening, maddening, and painful to live through and to treat. Infertility is rife with uncertainties. Most research on infertility has been based on theories of stress and coping, but it has neglected the concept of uncertainty that has been shown to affect significantly the infertility experience. The theory of uncertainty in illness is an appropriate alternative to stress and coping theories and should be considered when planning research or interventions for infertile women and couples.

The theory of uncertainty in illness addresses *the* key experience of infertile women and couples: wondering if a desired pregnancy will occur and if a treatment related pregnancy will be healthy. The theory provides a framework for understanding the stages of confusion that occur as the experience of infertility unfolds. Nurses are reminded (a) to consider the lack of symptom patterns, event familiarity, and event congruence that infertile women or couples experience; (b) to assess their cognitive capacity; (c) to share new and technical information about diagnosis, treatment and perinatal and pediatric outcomes after treatment in a manner appropriate and individualized for each patient; and (d) to direct patients to resources or structure providers for additional information and support.

The uncertainty in illness model is not a perfect fit for the experience of infertility. The various delineations within the appraisal phase of the model are least useful for research on nursing care to the infertile couple. This phase of the model could be modified to add the concept mastery and remove inference and illusion as the couple moves on to the theory's coping and adaptation stages.

Theory development is a dynamic process. And, uncertainty is a complex concept that continues to evolve and to be evaluated by nurses and other health care professionals who desire to reduce suffering and to improve patients' quality of life. The theory of uncertainty in illness provides nurses with a model that can help them understand the experience of infertility and the uncertainties associated with perinatal outcomes. It can generate testable hypotheses and guide nursing practice, particularly the development and implementation of nursing interventions. It allows health care professionals to make sense of the experience of infertility. Women ask themselves, "Will I get pregnant?" and

"Will I have a healthy child?" However, uncertainty does not end with a pregnancy or the birth of a healthy child. It is a constant – for everyone. Being aware of uncertainty and learning to embrace it are skills for a lifetime.

CHAPTER 4 METHODOLOGY

Research Aims and Questions

The overall goal of this secondary data analysis of a retrospective cohort study is to determine risk factors for adverse perinatal outcomes among women who have conceived a singleton pregnancy after a history of infertility. This will be accomplished by comparing outcomes between two groups of infertility patients (infertile women who conceived a singleton pregnancy as a result of infertility treatments, and infertile women who naturally conceived a singleton pregnancy after presenting for infertility treatment) to the outcomes of a group of women who did not have a history of infertility and conceived a singleton pregnancy spontaneously. The study aims are:

1. To identify the differences in health status, index pregnancy conditions, and perinatal outcomes (LBW and PTD) among three groups of women: fertile women who conceived a singleton pregnancy spontaneously, women who have a history of infertility who conceived a singleton spontaneously, and women who have a history of infertility who conceived a singleton pregnancy with treatment.
2. To determine whether there is a relationship between fertility conception status and PTD or LBW after controlling for maternal age and nulliparity.

Specific Aim 1 is an exploratory analysis of significant factors that may be predictive of adverse outcomes thereby requiring analyses in Specific Aim 2 to examine the main hypothesis of the study. The null hypothesis is: There is no difference in the frequency of PTD or LBW between the three groups of women: fertile women who

conceived a singleton pregnancy spontaneously; women with a history of infertility who conceived a singleton spontaneously; and women with a history of infertility who conceived a singleton pregnancy with treatment.

Study Design

This study is a secondary data analysis of a larger retrospective cohort study, Pregnancy and Pediatric Outcomes (funded by NICHD, 1-P01-HD3707-06). The original study was designed to examine pregnancy, labor and delivery, and childhood outcomes up to six years of age in 2,000 women with either a history of infertility or who conceived using a variety of infertility treatments, and comparing these outcomes to 2,000 fertile women in the general population in California.

Sample

Assembly of the Infertile Cohort

Fertility Drugs and Ovarian Cancer Study (Croughan-Minihane et al., 2001) was conducted to determine if women exposed to ovulation-induction agents (fertility drugs) are at increased risk for ovarian, breast, and uterine cancer as compared to infertile women not exposed to ovulation induction agents. The study team assembled a cohort of 51,318 women who had undergone evaluation or treatment for infertility between 1/1/65 and 1/1/98 in 15 California infertility clinics (Figure 2, p. 57). The 15 practices participating in the Fertility Drugs and Ovarian Cancer Study were selected on the basis of developing a collection of physicians who used a variety of methods for treating infertility, and who have high quality medical record information, and who treated

patients with varying types of infertility and who had a variety of demographic characteristics. Eleven of these practices are located in Northern California and the remaining four are in Southern California. For the purposes of the Fertility Drug and Ovarian Cancer Study, information abstracted from the medical records on each patient included: patient's full name and alias names; patient addresses and phone numbers; medical record number or facility ID information; birth date and Social Security Number (SSN).

Given the costs associated with medical record abstraction and quality assurance, eligibility for the Pregnancy and Pediatric Outcomes Study (Croughan, Camarano, Bernstein, Chamberlain, & Schembri, 2004; Croughan et al., 2006) was limited to the 11 Northern California practices. The 11 practices were composed of six private practices, a university-affiliated program that performed ART, and the four practices in the Kaiser Permanente Medical Care Program. Although Kaiser Permanente did not provide ART services at the time of this study, they did perform initial evaluations, diagnostic procedures, used ovulation induction agents, performed intrauterine inseminations, and, under certain circumstances, provided support services and medication for ARTs performed at other centers. Thus, the 11 participating healthcare facilities provided a broad array of patient demographic characteristics, patient reproductive histories, infertility diagnoses and infertility treatment modalities while simultaneously providing excellent medical record documentation of infertility diagnoses, treatments, and outcomes.

Identifying Pregnancies and Deliveries Among All Infertile Patients

The infertile cohort that had been assembled for the Fertility Drug and Ovarian Cancer Study was linked to the State of California Birth Statistical Master File and the State of California Fetal Death Statistical Master File to identify pregnancies and births of women in the infertile cohort. The Birth Statistical Master File is the most comprehensive file related to births in California. The data contained in this file are compiled from the information reported on live birth certificates registered in California each year. The file contains information related to the infant, the mother and father, as well as the medical data related to the birth. The Fetal Death Statistical Master File contains California's annual baseline fetal death data. The data in this file are obtained from fetal death certificates that are registered in California each year. This file contains information related to the fetus, the mother and father, as well as the medical data related to the fetal death. The Kaiser Permanente Medical Care Program provided the third database for identifying pregnancies and deliveries that occurred at Kaiser Northern California facilities among the infertile cohort to assure complete ascertainment of pregnancies and deliveries and to provide comparative data. Data from the Kaiser database contained information on prenatal care, delivery, and discharge records. For each of the linkages described above, matches between the infertility patient database and the above noted databases were classified as follows: definite matches (100% matching on name, maternal birth date, address, SSN or medical record number); probable matches (slight variation in one of the variables such as name spelling); or possible matches (2 or 3 items match). All matches were manually reviewed and additional documents retrieved to further judge "possible" matches. Once all non-definite matches were rectified, a

separate database was developed that contained data from the above data sources as well as from the original Fertility Drugs and Ovarian Cancer Study database for each patient identified as having a pregnancy or delivery, and who met the study eligibility criteria (described below). This new database was called the *Infertility Pregnancy Cohort Database* and contained information for the infertile patient and her fetus or child or children (as appropriate) including: full name, address, phone number, medical record number or facility ID number, birthdates, infertility diagnoses, infertility treatments, dates of treatment, and delivery facility. Women in the infertile cohort were sent letters from their infertility healthcare provider inviting them to participate in the study. If a woman agreed to participate, she was interviewed and asked to release medical record information for herself and her child(ren). Telephone interviews were conducted with each woman to confirm fertility status (i.e. history of infertility). In situations where a woman had more than one pregnancy during the study period, a random number generator was used to select the pregnancy that served as the index pregnancy for the study.

Conception with infertility treatment was defined as a conception resulting from one or more of the following treatments: medications to induce ovulation, intrauterine insemination, and ART with IVF, with or without intracytoplasmic sperm injection (ICSI). Conception without infertility treatment was defined as not having undergone any infertility treatment within two menstrual cycles or 60 days prior to the estimated day of conception.

Eligibility Criteria for the Infertile Pregnancy Cohort

Eligibility criteria for the infertile pregnancy cohort were: a pregnancy that lasted 20 weeks gestation or longer with a delivery or resolution of the pregnancy (miscarriage or fetal demise) that occurred in Northern California between January 1, 1994 and January 1, 1998. Women who were seen by an infertility clinic only once, or who did not receive treatment and conceived a pregnancy spontaneously were included in the study as a comparison group for the women who did receive treatment, allowing for an assessment of the possible independent effect of infertility and infertility treatment.

Secondary Analysis: Infertile Pregnancy Cohort

A random sample from the infertile pregnancy cohort was used to obtain a final study population of 2,000 women with a history of infertility who conceived a pregnancy that met the eligibility criteria. Of the 2,000 women in the infertile pregnancy cohort, 983 women with a history of infertility who sought infertility treatment at one or more of the 11 healthcare facilities in Northern California had a singleton pregnancy and therefore are included in this sub-study of the Pregnancy and Pediatric Outcomes Study.

Assembly of the Fertile Pregnancy Cohort

After identifying members of the infertile pregnancy cohort, the fertile pregnancy cohort was determined by searching the State of California Birth Statistical Master File and the State of California Fetal Death Statistical Master File for pregnancies that lasted 20 weeks gestation or longer (fetal deaths and live births). For each infertile woman

identified as having a gestation lasting 20 weeks or longer, the next three certificates for women delivering in the same geographic area were downloaded in the study database. The three certificates for fetal death or delivery lasting 20 weeks gestation or longer were then reviewed to maximize frequency matching of fertile women to infertile women according to fetal death date or delivery date (± 2 months), maternal age (± 2 years), and number of gestations. Women in the fertile cohort were sent letters inviting them to participate in the study. If a woman agreed to participate, she was interviewed and asked to release medical record information for herself and her child(ren). Telephone interviews were conducted with each woman to confirm fertility status (i.e. no history of infertility)

Eligibility Criteria for the Fertile Pregnancy Cohort

Each fertile cohort member met the following eligibility criteria: the woman did not have a history of infertility, did not use infertility services, and was a resident of Northern California at the time of the delivery or resolution of the pregnancy. The same criteria for resolving database linkage matches described previously for creating the infertile pregnancy cohort was used for creating the fertile pregnancy cohort. Of the 2,000 women in the fertile pregnancy cohort, 1008 women had a singleton pregnancy and were included in the sub-study.

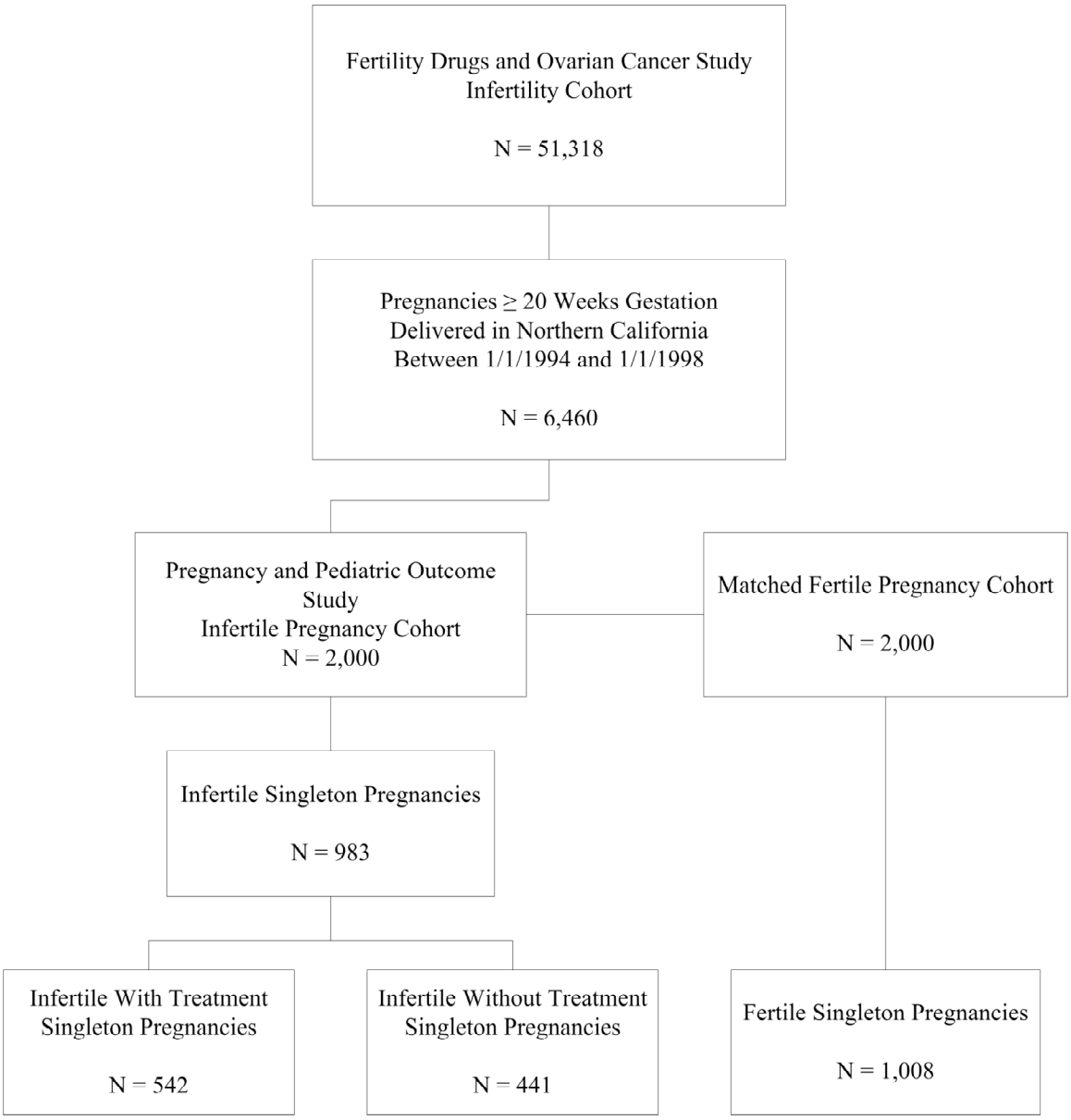

Figure 2*: Study Sample for the Risk of Preterm Delivery and Low Birth Weight in Singleton Pregnancies Conceived by Women with and without a History of Infertility Study*

Sources of Information

Multiple sources were used for obtaining complete information on infertility treatments, perinatal outcomes, and covariates of interest for all cohort members in this study. For the infertile pregnancy cohort members, data were collected from infertility clinic medical records, prenatal medical records, labor and delivery records, and neonatal and pediatric medical records. For the fertile pregnancy cohort members, data were collected from prenatal medical records and labor and delivery and neonatal and pediatric medical records.

Abstraction of Infertility Medical Records

Data collection began by reviewing the infertility medical records for each woman identified as an infertile pregnancy cohort member. Infertility treatment was defined as provision of services for evaluation, diagnosis, or treatment of infertility. Once eligibility was established, the medical record of the infertility practice was reviewed to ascertain exposures and PTD and LBW, check diagnostic methods and results, as well as to identify all other physicians who provided infertility treatment for a specific patient. Medical records were abstracted from all providers of infertility care for each woman. On average, infertile pregnancy cohort members saw two to three infertility service providers for infertility care.

Infertility diagnosis and treatment

Infertility diagnoses of interest consisted of male factor, ovulatory or ovarian dysfunction, uterine disorders, fallopian tube or pelvic damage, endocrine or hormonal disorders, cervical disorders, and unexplained infertility. Male factor infertility included

male diagnoses of azoospermia, oligospermia, decreased motility, abnormal morphology, congenital absence of the vas, retrograde ejaculation, varicocele, and/or vasectomy. Ovulatory or ovarian dysfunction included amenorrhea, oligomenorrhea, oligoovulation, hypermenorrhea, menorrhagia, polycystic ovarian syndrome, luteal phase defect or deficiency, hypothalamic amenorrhea or insufficiency, exercise-induced amenorrhea, advanced maternal age, premature ovarian failure, elevated FSH, perimenopause, menopause, diminished ovarian reserve, and/or poor response to gonadotrophins. Uterine disorders included myomas, adenomyosis, adenomyoma, intrauterine adhesions, Asherman's syndrome, in-utero DES exposure, uterine congenital anomalies such as mullerian anomaly, unicornate, bicornate and septate uterus, and/or uterine polyps. Fallopian tube or pelvic damage included blocked or removed fallopian tubes, hydrosalpinx, chronic salpingitis, history of ectopic pregnancy, history of tubal ligation, pelvic inflammatory disease, pelvic adhesions, and/or the presence of endometriosis. Endocrine or hormonal disorders included hyperprolactinemia, hyperthyroidism, hypothyroidism, other thyroid disorders, and/or adrenal gland disorders such as congenital adrenal hyperplasia. Cervical disorders included incompetent cervix, and/or hostile cervical mucus or mucus problems such as a poor post-coital test. Unexplained infertility included cases of infertility where no known cause for infertility could be detected.

All diagnostic tests and treatments for infertility were abstracted from medical records using a standardized data collection form. The infertility treatments of interest included: medication (fertility drugs or ovulation induction agents), intrauterine

insemination, IVF, intracytoplasmic sperm injection (ICSI), and medically induced fetal reduction.

Abstraction of Prenatal and Labor and Delivery and Neonatal Records

The next phase of medical record review consisted of the abstraction of prenatal, labor and delivery, and neonatal records for all cohort members. Information was collected on health status, index pregnancy conditions, and perinatal outcomes.

Health status

Health status information consisted of maternal age at the time of the index pregnancy, body mass index (BMI) prior to conception of the index pregnancy (calculated by using the maternal height and weight noted prior to the conception of the index pregnancy), obesity present at the time of index pregnancy (as noted in the medical record and defined as a BMI $\geq$ 30), a history of chronic hypertension present prior to the index pregnancy, Type I or Type 2 diabetes present prior to the index pregnancy, and heart disease present prior to the index pregnancy (any heart disease noted in the medical record, with the exception of mitral valve prolapse).

Index pregnancy conditions

Index pregnancy conditions information consisted of nulliparity at time of index pregnancy (a woman who had not completed one pregnancy with a fetus or fetuses who had reached the stage of fetal viability), nulligravida at the time of conception of the index pregnancy (a woman who is pregnant for the first time), any cigarette smoking during the index pregnancy, any alcohol consumption during the index pregnancy, gestational diabetes during the index pregnancy, excess weight gain during the index

pregnancy, pregnancy induced hypertension (PIH), intrauterine growth restriction (IUGR) (estimated weight below the 10th percentile for gestational age), small for gestational age (SGA) (weight below the 10th percentile for gestational age), sepsis (neonate diagnosed with sepsis), fetal or neonatal death.

Perinatal outcomes

Perinatal outcome information consisted of 1) low birth weight (LBW) defined as an infant that weighed < 2500 grams at birth; and 2) preterm delivery (PTD) defined as a pregnancy that ended prior to 37 completed weeks of gestation.

Medical Record Abstraction Form Development

Medical record abstraction form development began as a collaborative effort among the Principal Investigator, Co-Investigators, and consultants in the areas of reproductive endocrinology and infertility, urology, obstetrics, perinatology, and pediatrics, as well as members of the advisory board, which included psychologists, a medical ethicist, a medical anthropologist, and a health economist. Meetings occurred regarding the nature of the constructs to be measured (infertility diagnoses and treatments, health status, index pregnancy conditions, and perinatal outcomes) to both refine the parameters of data needed and to establish *content validity*. Once agreement was reached regarding the nature of the constructs, initial items and instruments were drafted, as existing measures did not exist in the literature. At that time, the instruments were reviewed by the core staff for comprehension and content. Instruments were then revised and pilot-tested in small samples of 20-25 infertility patients who had previously

participated in pilot tests for other studies related to infertility treatment. Instruments were revised a third time before being used for actual data collection.

Quality Assurance

In January 2000, eight medical record abstractors were hired and trained. Training consisted of one week of extensive classroom training in infertility, labor and delivery, and childhood health. The training was conducted by the Project Director with help from an obstetrician and a pediatrician. The classroom training was followed by two weeks of supervised abstracting on medical records and a complete re-abstraction by the Project Director until each abstractor had 100% agreement with the Project Director.

Once the abstractors were able to demonstrate accuracy, they began data collection in the field. Abstractors were instructed to flag all questions for review by the Project Director during field visits scheduled every two to three weeks. During the field visit, the Project Director reviewed all abstractions and performed a quality control check by re-abstracting 5% of all completed abstractions. The Project Director reviewed all errors (1% error rate) with the abstractor and noted the results of each quality assurance review in a logbook. Errors were categorized as either content errors or coding errors and recoded correctly. Medical record abstractors received continuing education by the Project Director every two months during data collection. Continuing education consisted of a one-day meeting every two months at the project office to review all study procedures associated with the medical record abstraction, to answer abstractor questions, and to provide support. Data were collected for the Infertile and Fertile Pregnancy

Cohorts from infertility clinic medical records, prenatal medical records, and labor and delivery records.

Data were double-entered and data were cleaned based on descriptive statistics.

Protection of Human Subjects

Approval from the University of California, San Francisco Committee on Human Research was obtained for the original study (Pregnancy and Pediatric Outcomes study CHR approval # H5702-1542-09), and a Modification Request for Minor and Administrative Changes was submitted in December 2008 for this secondary data analysis. IRB approvals also were obtained from the State of California and the Kaiser Foundation Research Instititue.

Data Analysis

Descriptive statistics were computed for all variables by fertility status group. To compare health status, index pregnancy conditions, and perinatal outcomes of LBW and PTD across three fertility status groups (fertile women, infertile women who conceived spontaneously, and infertile women who conceived with treatment) on all variables including, t-tests and ANOVA were conducted to compare mean scores on continuous variables and chi-square analyses on nominal variables across the groups. All analyses used *a priori p*-values of <. 05. SPSS 15 was used to conduct all analyses. Bonferroni post hoc contrasts were conducted on all variables which were significantly different across the three groups.

To determine which independent variables predict PTD and LBW modeled as dichotomous outcomes, logistic regression was performed. The data met the assumptions

of logistic regression. Logistic regression is a non-parametric method that requires no assumptions about the distribution of the independent (predictor) variables (Dawson & Trapp, 2004). However, assumptions of logistic regression include the use of a simple random sample and independence of observations. To determine potential *multicollinearity* between independent variables, Spearman rho correlations were conducted to assess overlap between independent variables.

The goal of this regression analysis was to find the best fitting and most parsimonious model to describe the relationship between each outcome or dependent variable (PTD, LBW) and the set of predictor or independent variables. Several steps were involved in identifying the final model.

Variables that were considered for inclusion in the model were those that had associations with PTD or LBW showing $p \leq .20$ in bivariate analyses. Clinically significant and potentially confounding variables were identified through a review of the literature and included maternal age and nulliparity. These clinically significant variables were included in all models as potential confounders.

CHAPTER 5 RESULTS

This chapter summarizes the results of the study based on each research aim.

Aim 1

The first aim was to identify the differences in health status, index pregnancy conditions, and perinatal outcomes (LBW and PTD) among three groups of women: fertile women who conceived a singleton pregnancy spontaneously, women who have a history of infertility who conceived a singleton spontaneously, and women who have a history of infertility who conceived a singleton pregnancy with treatment.

Research Question: Does the frequency of PTD or LBW differ between the three groups of women: fertile women who conceived a singleton pregnancy spontaneously; women with a history of infertility who conceived a singleton pregnancy spontaneously; and women with a history of infertility who conceived a singleton pregnancy with treatment.

Null Hypothesis: There is no difference in the frequency of PTD or LBW between the three groups of women: fertile women who conceived a singleton pregnancy spontaneously; women with a history of infertility who conceived a singleton pregnancy spontaneously; and women with a history of infertility who conceived a singleton pregnancy with treatment.

The health status, index pregnancy conditions, and perinatal outcomes of LBW and PTD of fertile women who conceived a singleton pregnancy spontaneously (n =

1008), women who had a history of infertility who conceived a singleton pregnancy spontaneously (n = 441), and women who had a history of infertility who conceived a singleton pregnancy with treatment (n = 542) are listed in Table 1.

Health Status

Maternal age: The mean age of the fertile comparison group was 32.87 (SD 5.1) years, of the infertile without treatment group was 35.25 (SD 4.7) years, and of the infertile with treatment group was 36.3 (SD 4.93) years. The three groups were significantly different with regard to age (F (2) = 93.7, $p < .05$) , with the fertile comparison group significantly younger than the infertile with treatment group.

Body Mass Index (BMI): The mean BMI for the fertile comparison group was 24.19 (SD = 5.0), for the infertile without treatment group was 24.89 (SD 5.5), and for the infertile with treatment group was 24.67 (SD 5.4). There was no statistically significant difference (F (2) = 2.78, $p = .06$) between the three groups on BMI.

Obesity: Forty-three women (4.3%) in the fertile comparison group 10 women (2.3%) in the infertile without treatment group, and 31 women (5.8%) in the infertile with treatment group were obese. There was a significant difference between the groups with regard to obesity frequency (chi-square (2) 7.23, $p < .05$). There were more women in the infertile with treatment group than women in the infertile without treatment group who were obese.

Chronic Hypertension: Twelve women (1.2%) in the fertile comparison group, 3 women (.7%) in the infertile without treatment group, and 8 women (1.5%) in the infertile with treatment group had chronic hypertension. There was no significant

difference (chi-square (2) = 1.38, p = .50) between the three groups in the frequency of chronic hypertension prior to the index pregnancy.

Diabetes: Four women (0.4%) in the fertile comparison group, 5 women (1.1%) in the infertile without treatment group, and 5 women (0.9%) in the infertile with treatment group had a diagnosis of diabetes prior to the conception of the index pregnancy. There was no significant difference (chi-square (2) = 2.90, p = .234) between the groups in the frequency of diabetes prior to the index pregnancy.

Heart Disease: Three women (.3%) in the fertile comparison group, 3 women (.7%) in the infertile without treatment group, and 3 women (.6%) in the infertile with treatment group had been diagnosed with heart disease prior to the index pregnancy. There was no significant difference (chi-square (2) 1.17, p = .56) between the three groups in the frequency of heart disease.

Index Pregnancy Conditions

Nulliparous: Five hundred ninety women (41.5%) in the fertile comparison group, 265 women (39.8%) in the infertile without treatment group, and 322 women (59.7%) in the infertile with treatment group were nulliparous prior to the index pregnancy. The three groups differed significantly (chi-square (2) 56.16, $p < .05$). With regard to nulliparity: there were more women in the fertile with treatment group who were nulliparous prior to the index pregnancy compared to the fertile comparison group and the infertile without treatment group.

Nulligravida: Two hundred twenty-six women (22.4%) in the fertile comparison group, 85 women (19.3%) in the infertile without treatment group, and 157 (29%) women in the infertile with treatment group were nulligravida at the time of the index pregnancy.

There was a significant difference between the three groups (chi-square (2) 14.04, p = .001). There were more women in the infertile with treatment group than women in either the infertile without treatment group or the fertile comparison group who were nulligravida at the time of the index pregnancy.

Smoking During Index Pregnancy: Sixty-five women (6.8%) in the fertile comparison group, 8 women (2.1%) in the infertile without treatment group, and 9 women (1.9%) in the infertile with treatment group smoked during the index pregnancy. There was a significant difference (chi-square (2) 24.27, $p < .05$) in the rate of smoking between the three groups. There were more women in the fertile comparison group than in the infertile with or without treatment groups who smoked.

Alcohol Consumption During Index Pregnancy: One hundred thirteen women (12.1%) in the fertile comparison group, 50 women (13.4%) in the infertile without treatment group, and 35 women (7.6%) in the infertile with treatment group consumed alcohol during the index pregnancy. There was a significant difference (chi-square (2) 8.56, $p <$ .05) between the groups on alcohol consumption frequency. There were more women in the fertile comparison group and the infertile without treatment group who consumed alcohol than in the infertile with treatment group.

Gestational Diabetes: Eighty-seven women (8.7%) in the fertile comparison group, 22 women (5.1%) in the infertile without treatment group, and 51 women (9.8%) in the infertile with treatment group were diagnosed with gestational diabetes during the index pregnancy. There was a significant difference in the frequency of gestational diabetes between the three groups of women (chi-square (2) 7.32, p = .03). There were more

women in the infertile with treatment group than women in the infertile without treatment group with gestational diabetes during the index pregnancy.

Excess Weight Gain: Seven women (.7%) in the fertile comparison group, 3 women (.7%) in the infertile without treatment group, and 2 women (.4%) in the infertile with treatment group had excess weight gain during the index pregnancy. There was no significant difference (chi-square (2) .674, $p = .71$) in the frequency of excess weight gain during the index pregnancy between the three groups of women.

Pregnancy Induced Hypertension (PIH): Sixty-three women (6.3%) in the fertile comparison group, 25 women (6%) in the infertile without treatment group, and 35 women (6.8%) in the infertile with treatment group had PIH during the index pregnancy. There was no significant difference (chi-square (2) .293, $p = .86$) in the frequency of PIH between the three groups of women.

Intrauterine Growth Restriction (IUGR): Sixteen women (1.6%) in the fertile comparison group, 11 women (2.5%) in the infertile without treatment group, and 19 women (3.5%) in the infertile with treatment group developed IUGR during the index pregnancy. There was no significant difference (chi-square (2) 5.83, $p = .054$) in the frequency of IUGR between the three groups of women.

Small For Gestational Age (SGA): Eleven women (1.1%) in the fertile comparison group, 9 women (2.1%) in the infertile without treatment group, and 14 women (2.7%) in the infertile with treatment group delivered a SGA infant during the index pregnancy. There was no significant difference (chi-square (2) 5.31, $p = .070$) between the three groups of women.

Neonatal Sepsis: Ten women (1%) in the fertile comparison group, 6 women (1.4%) in the infertile without treatment group, and 9 women (1.7%) in the infertile with treatment group had an infant diagnosed with sepsis. There was no significant difference (chi-square (2) 1.44, $p = .49$) in the frequency of neonatal sepsis during the index pregnancy between the three groups of women.

Fetal or Neonatal Death: Seven women (.8%) in the fertile comparison group, 4 women (1.1%) in the infertile without treatment group, and 9 women (2%) in the infertile with treatment group experienced a fetal or neonatal loss during the index pregnancy. There was no significant difference (chi-square (2) 3.55, $p = .17$) in the frequency of fetal or neonatal death during the index pregnancy between the three groups of women.

Perinatal Outcomes of PTD and LBW

PTD: Sixty-five women (6.6%) in the fertile comparison group, 29 women (6.8%) in the fertile without treatment group, and 42 women (8.1%) in the fertile with treatment group gave birth to a singleton infant before 37 weeks gestation during the index pregnancy. There was no significant difference (chi-square (2) 1.23, $p = .541$) in the frequency of PTD between the three groups of women. Of the pregnancies that were premature, some were very preterm (VPT) and delivered prior to 32 weeks gestation, six (.59%) of these VPT deliveries were in the fertile comparison group, 5 (1.1%) VPT deliveries were in the infertile with no treatment group, and 8 (1.4%) VPT deliveries were in the infertile with treatment group. There was not a significant difference between the groups on VTP deliveries ($p = .198$).

LBW: Sixty-three women (6.4%) in the fertile comparison group, 37 women (8.6%) in the infertile without treatment group, and 56 women (10.8%) in the infertile with treatment group delivered LBW infants during the index pregnancy. There was a significant difference in the frequency of LBW among the three groups of women (chi-square (2) 9.12, $p = .01$). There were more women in the infertile with treatment group compared to the fertile comparison group who delivered a LBW infant. Of the pregnancies that were LBW, some infants weighed less than 1500 g and were considered very LBW (VLBW). Twenty eight (2.7%) of these VLBW infants were in the fertile comparison group, 19 (4.3%) VLBW infants were in the infertile with no treatment group, and 31 (5.7%) VLBW infants were in the infertile with treatment group. There was a significant difference in the frequency of VLBW among the three groups of women (chi-square (2) 8.85, $p = .012$). There were more women in the infertile with treatment group than women in the fertile comparison group who gave birth to a VLBW infant.

Summary of results comparing the three groups

Women who were members of the three groups (fertile comparison, infertile without treatment, and infertile with treatment) were compared on demographic characterisitics, chronic health conditions, and index pregnancy conditions (Table 1). With regard to demographic characteristics, the fertile comparison, infertile without treatment, and infertile with treatment groups differed with regard to age; the infertile with treatment group were 1.1 years older than the infertile without treatment group, and 3.47 years older than the fertile comparison group. With regard to chronic health conditions, the three groups differed significantly on rate of obesity, with the infertile

with treatment group being more likely to be obese compared with the infertile without treatment group and the fertile group. In regard to index pregnancy conditions, the groups differed with respect to nulliparity, nulligravity, smoking and alcohol consumption during the index pregnancy, and the development of gestational diabetes during the index pregnancy. Specifically, the infertile with treatment group was more likely to be nulliparous, nulligravida, and obese, and to develop gestational diabetes during the index pregnancy as compared to both the infertile without treatment group and the fertile comparison group. The fertile comparison group was more likely to smoke during the index pregnancy than both the infertile without treatment and the infertile with treatment groups. Both the fertile comparison group and the infertile without treatment group were more likely to consume alcohol during the index pregnancy when compared to the infertile with treatment group. With regard to the perinatal outcomes of the index pregnancy, women in the infertile with treatment group were more likely to give birth to a LBW infant than women in the fertile comparison group; however, there was no difference in the rate of PTD between the three groups.

Unique characteristics of the infertile pregnancy cohort

The infertility diagnoses of women who have a history of infertility who conceived a singleton spontaneously and women who have a history of infertility who conceived a singleton pregnancy with treatment are listed in Table 2. The infertility treatments utilized by women who have a history of infertility who conceived a singleton pregnancy with treatment are listed in Table 3.

Infertility diagnoses of the Infertile Pregnancy Cohort

Male Factor: Eighty-four women (19.4%) in the infertile without treatment group, and 171 women (32.3%) in the infertile with treatment group had a partner with male factor infertility. There was a significant difference in the frequency of male factor infertility between the two groups of women (chi-square (1) 20.6, $p < .05$). There were more women in the infertile with treatment group compared to the infertile without treatment group who had a partner with male factor infertility.

Ovarian Dysfunction: Two hundred thirty-nine women (55.1%) in the infertile without treatment group, and 354 women (66.9%) in the infertile with treatment group had ovarian dysfunction. There was a significant difference in the frequency of ovarian dysfunction between the two groups of women (chi-square (1) 20.6, $p < .05$). There were more women in the infertile with treatment group compared to the infertile without treatment group who had ovarian dysfunction.

Uterine Disorders: Eighty-six women (19.8%) in the infertile without treatment group, and 117 women (22.1%) in the infertile with treatment group had uterine disorders. There was no significant difference in the frequency of uterine disorders between the two groups of women (chi-square (1) .76, $p = .39$).

Fallopian Tube or Pelvic Damage: One hundred sixty-two women (37.3%) in the infertile without treatment group, and 186 women (35.2%) in the infertile with treatment group had fallopian tube or pelvic damage. There was no significant difference in the frequency of fallopian tube or pelvic damage between the two groups of women (chi-square (1) .49, $p = .49$).

Endocrine or Hormonal Disorders: Fifty women (11.5%) in the infertile without treatment group, and 56 women (10.6%) in the infertile with treatment group had

endocrine or hormonal disorders. There was no significant difference in the frequency of endocrine or hormonal disorders between the two groups of women (chi-square (1) .21, p = .65).

Cervical Disorders: Twenty-eight women (6.5%) in the infertile without treatment group, and 52 women (9.8%) in the infertile with treatment group had cervical disorders. There was no significant difference in the frequency of cervical disorders between the two groups of women (chi-square (1) 3.57, p = .06).

Unexplained Infertility: Twenty-five women (5.8%) in the infertile without treatment group, and 26 women (4.9%) in the infertile with treatment group had unexplained infertility. There was no significant difference in the frequency of unexplained infertility between the two groups of women (chi-square (1) .34, p = .56).

Summary of results comparing the three groups

Women who were members of the infertile with or without treatment groups were compared on infertility diagnoses. Women in the infertile with treatment group were likely to have an ovarian or ovulatory dysfunction or to have a partner with male factor infertility.

Infertility treatment type for the infertile with treatment group

Medications: Four hundred and seven women (76.9%) in the infertile with treatment group used medications to conceive the index pregnancy.

Intrauterine Insemination (IUI): Two hundred and fifteen women (40.6%) in the infertile with treatment group used IUI to conceive the index pregnancy.

In vitro Fertilization (IVF): Sixty-four women (12.1%) in the infertile with treatment group used IVF to conceive the index pregnancy.

Intracytoplasmic Sperm Injection (ICSI): Twenty-four women (4.5%) in the infertile with treatment group used ICSI to conceive the index pregnancy.

Fetal Reduction: Five women (.9%) in the infertile with treatment group underwent pregnancy reduction to reduce a multiple gestation pregnancy during the index pregnancy.

Aim 2

The second Specific Aim of this study was to determine whether there was a relationship between fertility conception status and PTD or LBW after controlling for potentially confounding variables.

Research Question: Does fertility conception status predict PTD or LBW in singleton pregnancies?

Null Hypothesis: There is no difference in the frequency of PTD or LBW between the three groups of women: fertile women who conceived a singleton pregnancy spontaneously; women who have a history of infertility who conceived a singleton pregnancy spontaneously; and women who have a history of infertility who conceived a singleton pregnancy with treatment.

A binary logistic regression with best model construction was performed to assess the impact of a number of factors on the likelihood that a singleton pregnancy would result in a LBW infant. The model contained six independent variables including one continuous variable: mother's age; and five nominal variables: nulliparity, infertility with treatment and infertility without treatment (both groups compared to fertile comparison group), obesity during index pregnancy, and gestational diabetes during index pregnancy.

Smoking and alcohol consumption during the index pregnancy added to the model and were non-significant predictors. Thus these variables were not included in the final model. Nulliparity and nulligravity were highly correlated with each other (r = .601; see table 4) and a review of the literature showed that most studies of LBW in women with a history of infertility used nulliparity, so nulliparity was included in this model.

Final multivariate logistic model with LBW as outcome

The final model with predictor variables and LBW as the outcome variable was statistically significant, chi-square (6, N = 1878) = 14.43, p = .025, indicating that the model was able to distinguish between women who did and did not give birth to a LBW infant. The Hosmer and Lemeshow Test was not significant (chi-square = 5.379 (df 8) p = .716), indicating that the data fit the model. The model as a whole explained between 0.8% (Cox and Snell R square) and 1.8% (Nagelkerk R square) of the variance in LBW status, and correctly classified 92% of cases. As shown in Table 5, only two of the independent variables made a unique, statistically significant contribution to the model. The strongest predictor of LBW was infertility treatment. Women with a history of infertility who underwent infertility treatment to conceive their pregnancy were 1.55 (CI 1.03, 2.34) times greater odds to give birth to a LBW infant than fertile women who conceived a pregnancy spontaneously, controlling for maternal age, nulliparity, obesity, and gestational diabetes. Infertile woman who conceived a pregnancy without treatment and fertile woman have similar risk of LBW infants (p = .247) after controlling for maternal age, nulliparity, obesity, and gestational diabetes. The odds ratio of 1.51 (CI 1.07, 2.14) for nulliparity indicates that women who gave birth to a LBW infant had a 1.51 times greater odds to be nulliparous, after controlling for maternal age, infertility

treatment, obesity, and gestational diabetes. Therefore, infertility treatment and nulliparity appear to be independent predictors of LBW for women who have infertility compared to women with a history of infertility who conceived a pregnancy without treatment. Overall, infertile woman who need treatment to conceive appear to have a higher risk of LBW compared to women who do not need treatment to conceive.

Final multivariate logistic model with PTD as outcome

The final model with predictor variables and PTD as the outcome variable was not statistically significant, chi-square (6, N = 1878) = 11.684, $p = .069$, indicating that the model was not able to distinguish between women who did and did not give birth to a PTD infant. As shown in Table 6, only one of the independent variables made a unique, statistically significant contribution to the model. The only predictor of PTD was nulliparity. The odds ratio of 1.72 (CI 1.2, 2.5) for nulliparity indicates that women who gave birth to a PTD infant had a 1.72 times greater odds to be nulliparous after controlling for maternal age, infertility treatment, obesity, and gestational diabetes. Overall, women with a history of infertility who conceive a singleton pregnancy appear to have the same risk of PTD compared to women who do not a history of infertility.

CHAPTER 6 DISCUSSION OF FINDINGS

The findings from this Northern California population-based study provide new insights into the potential mechanisms that may influence the perinatal outcomes of IVF pregnancies. By comparing outcomes between two groups of infertility patients (infertile women who conceived a singleton pregnancy as a result of infertility treatments, and infertile women who conceived a singleton pregnancy naturally after presenting for infertility treatment) with the outcomes of a group of women who did not have a history of infertility and conceived a singleton pregnancy spontaneously, we were able to look at the effects of both infertility and fertility treatment on PTD and LBW. This chapter will present a discussion of the study findings, their implications for clinical practice, study limitations and strengths, and needs for future research.

Overall these findings suggest that women with a history of infertility who undergo infertility treatment and conceive a singleton pregnancy are not at increased risk for PTD, but appear to be at increased risk for giving birth to a LBW infant, and should be monitored closely during pregnancy for restricted neonatal growth. These findings also suggest that women who have a history of infertility and are nulliparous at the time of conception are at increased risk of giving birth to a LBW infant compared to fertile women who conceive spontaneously and should be monitored closely for signs of restricted neonatal growth. Women with a history of infertility in this sample do not appear to be at increased risk of preterm delivery.

Significant Variables

One of the most significant complications associated with infertility treatment and assisted reproductive technology (ART) is the high frequency of multiple birth gestations and associated poor perinatal outcomes (Chung et al., 2006; Keirse & Helmerhorst, 1995). Our study sought to determine if singleton pregnancies conceived by women with a history of infertility who conceived either with infertility treatment or spontaneously are also at increased risk for PTD or LBW. Comparison of the three groups of women: infertile women who conceived a singleton pregnancy as a result of infertility treatment; infertile women who conceived a singleton pregnancy naturally after presenting for infertility treatment; and women who did not have a history of infertility and conceived a singleton pregnancy spontaneously identified several significant underlying differences between the groups, including maternal age, parity, gestational diabetes, obesity, and smoking and alcohol consumption.

Maternal Age

A trend of women delaying childbearing until later in life has developed, especially among more educated and financially stable women worldwide (Chan & Lao, 2008). In our study population, we found that maternal age increased with level of infertility and treatment status. The fertile women had a mean age of 32.87 years (SD 5.1), the infertile with no treatment group had a mean age of 35.25 years (SD 4.74), and the infertile with treatment group had a mean age of 36.34 years (SD 4.93).

Maternal age is a strong predictor of infertility, with fecundity decreasing and the risk of miscarriage increasing with maternal age (Adamson & Baker, 2003; Menken,

Trussell, & Larsen, 1986; Usta & Nassar, 2008). Pregnancies of women of advanced maternal age (defined as greater than 30-35 years of age) have traditionally been regarded as higher risk for hypertensive disorders, gestational diabetes, antepartum hemorrhage, and maternal and newborn complications (Bianco et al., 1996; Chan & Lao, 2008; Ozalp, Tanir, Sener, Yazan, & Keskin, 2003; Usta & Nassar, 2008; S. Ziadeh & Yahaya, 2001; S. M. Ziadeh, 2002), thus making maternal age a potential confounding factor for adverse perinatal outcomes. In the perspective of the literature, nearly all studies controlled for maternal age. Two studies that specifically looked at maternal age found that age was not associated with obstetric complications in ART assisted pregnancies (Schieve et al., 2002; Suzuki & Miyake, 2008). Suzuki and Miyake (2008) did not find age to be a factor in obstetric outcomes of pregnancy induced hypertension, placental abnormalities, PTD, or neonatal asphyxia in nulliparous women aged 35 and older with singleton pregnancies conceived by IVF, when compared to younger women, leading the authors to conclude that obstetric complications in pregnancies conceived by IVF may be attributed to mechanisms other than those dependent on maternal age. Schieve et al. (2002) found that singleton infants born at 37 weeks gestation or later and conceived with ART had a LBW risk that was 2.6 times that in the general population; however, this difference was not explained by maternal age. Maternal age was adjusted for in this study; however, it did not add significantly to the model and did not independently predict LBW.

Parity

Nulliparous women, defined as women who have never given birth to a child that reached viability (Oxorn & Foote, 1986) are known to give birth to lower weight infants

(Blickstein, Rhea, & Keith, 2005; Kus et al., 2008). Nulliparity also is associated with an increased rate of abnormal labor or dystocia (Kaergaard, Olsen, Ottesen, & Dykes, 2009), which correlates with labor interventions and cesarean section deliveries, as well as adverse perinatal outcomes (ACOG, 2003). Most perinatal outcome studies controlled for or adjusted for parity, and two studies (Bergh et al., 1999; Gissler et al., 1995) described their populations in terms of parity, finding that women who underwent IVF had fewer previous pregnancies and births than their fertile comparisons. Schieve et al. (2002) found that singleton infants born at 37 weeks gestation or later and conceived with ART had a LBW risk that was 2.6 (CI: 2.4, 2.7) times that in the general population; however, this difference was not explained by parity. Luke et al. (2004) found that among nulliparous women, the risk for preeclapmsia was increased in both spontaneously conceived twin and ART twin pregnancies, regardless of the method of conception. Thus, parity may be a marker for severity of infertility. In our study, women who underwent treatment to conceive were more likely to be nulliparous than either fertile women or women with a history of infertility who conceived without treatment. Nulliparity was added in the final model and did predict LBW.

Gestational diabetes

Gestational diabetes may be associated with many fetal and maternal complications (Oxorn & Foote, 1986). These complications include delivery of both large for gestational age infants when the mother has elevated blood glucose levels, and PTD potentially leading to a LBW infant when the pregnancy must be terminated before 37 weeks gestation due to poorly controlled diabetes or abnormal antepartum testing

results. One study (Maman et al., 1998), designed to look at obstetric outcomes of singleton pregnancies conceived by IVF and ovulation induction compared with those conceived spontaneously, found that even after controlling for maternal age, gestational age, and parity, singleton pregnancies conceived by IVF and ovulation induction are at increased risk for maternal gestational diabetes. In our study population, infertile women who conceived without treatment had less gestational diabetes than either the infertile women who conceived with treatment or the fertile conception group. Although gestational diabetes did not predict LBW in the current study, perhaps women who are prone to gestational diabetes have a lower reproductive potential and therefore a greater incidence of infertility.

Obesity

Obesity is the most common chronic disease in the U.S. and it contributes to a large number of health problems, including type II diabetes, hypertension, and coronary heart disease, as well as increases in breast, endometrial, ovarian, and colon cancer (ASRM, 2008; Cedergren, 2004; J. L. Weiss et al., 2004). Maternal obesity is associated with menstrual cycle irregularities, infertility and adverse perinatal outcomes, including pregnancy loss, preeclampsia, gestational diabetes, cesarean delivery, and increased risk of birth defects (Adamson & Baker, 2003; ASRM, 2008; Cedergren, 2004; Fedorcsak et al., 2004; J. L. Weiss et al., 2004). Although obesity is a potential confounding variable, it has only been controlled for in a few perinatal outcome studies (Luke et al., 2004). In our study, both women in the infertile with treatment group and the fertile comparison group had a greater frequency of obesity compared to the infertile without treatment

group, although it did not predict LBW. Perhaps the lower rate of obesity in the infertile without treatment group was an advantage to women with sub-fertility, allowing them to eventually conceive a pregnancy without the assistance of treatment.

Implications

This study's objectives included determining the extent of PTD and LBW in women with a history of infertility with or without a history of infertility treatment, and identifying risk factors that increase a woman's risk for these adverse perinatal outcomes. A major aim of this study was to identify subgroups of women who might be at high risk for adverse outcomes such that women could be well informed and clinical care could be adjusted accordingly. The first step in this process was to determine if there is an association between having a history of infertility or undergoing infertility treatment and the development of PTD or LBW. Cohort studies have previously been conducted in several countries to detect increases in adverse perinatal outcomes (Australian In Vitro Fertilisation Collaborative Group, 1985; MRC Working Party on Children Conceived by In Vitro Fertilisation, 1990; Tan et al., 1992). Tan and colleagues calculated a relative risk for the population of singleton IVF pregnancies conceived at two British clinics and found that women who conceived through IVF were 1.8 (CI: 1.3, 2.4) times more likely to deliver a preterm infant (< 37 weeks) than women who conceived naturally. Other studies reported similar findings of increased adverse perinatal outcomes for IVF conceived pregnancies (Australian In Vitro Fertilisation Collaborative Group, 1985; MRC Working Party on Children Conceived by In Vitro Fertilisation, 1990), suggesting that an association exists between exposure to IVF and adverse perinatal outcomes.

In our initial univariate analysis, we did find an association between fertility conception status and LBW, but not PTD. We also found that there were significant differences in the characteristics of women between the fertility conception status groups. Maternal age increased as fertility status decreased, and women in the infertile with treatment group had fewer previous pregnancies or deliveries, more gestational diabetes, and more obesity than women who conceived without treatment. Women who utilized treatment to conceive also may be more highly motivated to become parents, and experience their pregnancies as more precious and vulnerable, as demonstrated by these women's lower use of alcohol and smoking during pregnancy.

When an association is found between an exposure and a disease, the association may be the result of confounding by a third factor that is both a risk factor for the disease, and is associated with the disease (Gordis, 2004). Confounding describes the interrelationships between risk factors and an outcome, and can be addressed in the design of a study by using matching, or during the analysis phase by using stratification or adjustment. Known confounders for adverse perinatal outcomes include maternal age, parity, and multiple gestation. In our multivariate analysis, we adjusted for both maternal age and parity, and evaluated only singleton gestations as a way to avoid the effects of multiple birth gestations.

Because the association between fertility status and LBW was identified in our study population, we then tried to identify characteristics or risks that increased the probability of developing LBW. Logistic regression was utilized to determine which variables affect the probability of LBW. Interpretation of the final logistic regression model from the current study reveals that infertility treatment and nulliparity were the

factors most significantly associated with an increased likelihood of delivering a LBW infant after a history of infertility. While nulliparity was predictable from the literature, infertility treatment was less so. While several studies did find an increased risk of LBW in singleton pregnancies of women who underwent treatment to conceive (Jackson et al., 2004; Schieve et al., 2002; Tan et al., 1992), others did not (Reubinoff et al., 1997; Verlaenen et al., 1995). This contrast in findings may indicate that the effect size of infertility treatment on LBW may be small and not detectable in all studies.

It is prudent to ask the question: Is the infertility treatment the cause of LBW or is the LBW due to factors that necessitate the treatment? Several studies have tried to answer this very question. Romundstad et al. (2008) looked at women in Norway who had conceived at least one child spontaneously and another after ART. They found that birthweight and gestational age did not differ among infants of women who had conceived both spontaneously and after ART, although ART perinatal outcomes were significantly worse than spontaneous conceptions in the general population. These findings led the authors to conclude that the adverse outcomes in the ART population could be attributed to the factors leading to infertility, rather than to factors related to the reproductive technology.

An earlier study (Sundstrom et al., 1997) compared treatment related and treatment independent pregnancies in infertile couples by infertility diagnosis and treatment type. The treatments included in the study were ovulation induction medication, tubal surgery, intra-uterine insemination, and IVF. Of note, woman who attended the same clinic for treatment, yet never delivered a pregnancy, were significantly older compared with those with a delivery. Among the couples with a

treatment related delivery, the dominant infertility diagnoses were tubo-peritoneal pathology (43.5%) and ovulatory disorders (38%), whereas unexplained infertility was the predominant diagnosis (63%) among couples who conceived independent of treatment. Irrespective of diagnosis, the perinatal outcomes of LBW and PTD were greater in the treatment related group.

In the current study, we attempted to distinguish between different variables that might help us to answer that question. There are several significant differences between women in our study who required treatment to conceive a pregnancy and those who did not require treatment to conceive after a period of infertility. Women who underwent treatment to conceive were more likely to have a diagnosis of ovarian or ovulatory dysfunction, and their male partners were more likely to have male factor infertility. Both of these diagnoses are related to the gametes or eggs and sperm being used to create a pregnancy. Additionally, women who required treatment to conceive were older than women who conceived spontaneously. Some reports indicate that delayed pregnancy is associated with an increased proportion of LBW infants (Jacobsson, Ladfors, & Milsom, 2004; Usta & Nassar, 2008).

Implications for Future Research

By identifying factors that may increase the risk of a disease or adverse outcome, steps can be taken to decrease the probability of the development of a disease and to provide the foundation for developing public policy on health problems.

The problem of adverse perinatal outcomes, such as preterm birth and low birth weight infants, prompted the Institute of Medicine to convene a committee to assess the

current state of the science (IOM Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). The committee identified three national priorities: to establish multidisciplinary research centers, to conduct research, and to study and inform public policy. The priority to conduct research included a recommendation to "investigate the causes of and consequences for preterm births that occur because of fertility treatments" (IOM Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007, p. 17). Specifically, the committee recommended that researchers "develop comprehensive registries for clinical research, with particular emphasis on obtaining data on gestational age and birth weight….and distinguish multiple gestations from singleton gestations" (IOM Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007, pp.17-18). The Pregnancy and Pediatric Outcomes study (Croughan et al., 2006) created the registry that was utilized for the current study. The next step in our program of research will be to determine if there are specific infertility treatments within our infertile with treatment cohort that are associated with an increased risk of LBW. Additionally we plan to conduct a path analysis of the relationships between pregnancy complications, L & D complications, neonatal complications, and adverse childhood outcomes. We will continue to follow these children through adolescence and into adulthood.

Implications for Nursing Practice in Perspective of the Theory of Uncertainty in Illness

Pregnancy is a time of increased vulnerability and uncertainty for all women (Field & Marck, 1994; Mercer, 2006; Mercer & Walker, 2006; Smee, 2008), therefore the theoretical framework for this study, Theory of Uncertainty in Illness applies to women

with a history of infertility who are concerned about the conception, health and survival of their unborn child or children**.** The nursing implications of this study's results address *the* key experiences of infertile women and couples: wondering if a desired pregnancy will occur and if that pregnancy will produce a healthy child.

Reproductive mechanisms can be affected when one is stressed (Sapolsky, 1998) and the research supports the concept of infertility and its treatment as a major stressor (Domar et al., 1992). Infertile women report that infertility is stressful and is possibly the worst crisis of their lives, experienced as more significant than divorce or the loss of a parent (Mahlstedt et al., 1987) and research documents that women with infertility can have the same levels of depression as those with cancer, heart disease, or HIV infection (Domar, Zuttermeister, & Friedman, 1993). Stress is associated with several mechanisms that disrupt fertility including: elevated levels of adrenal androgens and prolactin levels which can delay or prevent ovulation from occurring; and reduction of progesterone levels which inhibits development of the uterine lining (Sapolsky, 1998) thereby affecting implantation of the embryo and possibly inhibiting fetal growth.

While infertility often (18.9% of the time) resolves in a spontaneously conceived pregnancy, some woman must undergo treatment to conceive (Sundstrom et al., 1997) and stress also has an impact during treatment. The infertility work-up includes medical examinations, questions about sexual behavior, and a technical approach to reproduction. Many people feel embarrassed at discussing their sexual practices with a healthcare provider (Diamond, 1999) and find physical exams and diagnostic procedures to be uncomfortable or even painful, adding to the level of experienced stress. It has been suggested that this increased uncertainty and stress associated with treatment may also

be associated with treatment failure (Sapolsky, 1998). Perhaps they also are associated with the increased risk of adverse perinatal outcomes such as LBW.

Two phases of the Theory of Uncertainty in Illness that are extremely relevant to the experience of infertility are coping and adaptation. Two studies suggest that group psychological interventions may be an effective way to help people deal with the uncertainty and stress associated with infertility treatment and may even lead to increased pregnancy rates in infertile women. One study (McNaughton-Cassill et al., 2000) was designed to assess the efficacy of couples stress management groups offered to patients undergoing IVF treatment at a Texas medical center. Couples in IVF treatment were given the option of participating in a biweekly stress management group. One or both members of 17 couples participated in the program in one of four group cycles. A cognitive behavioral treatment model was used to help couples process their feelings and cognitions about the impact of infertility on their life and explore their expectations about their future options for becoming parents. Couples were asked to anonymously evaluate the efficacy of the group after they had completed their IVF cycle. Participants reported that the group helped them deal with the stress of infertility and that they valued the social bonds they formed with other group members. The researchers concluded that brief focus group therapy, offered while couples are undergoing IVF, is an effective way to help people deal with the stress of infertility treatment. A number of common themes and concerns emerged from the groups in this study. Couples entering the group began by relating their infertility histories and the anguish that they felt due to the need for infertility treatment. The first theme to emerge was that hearing the stories of other group members had a normalizing effect and helped people to feel less isolated. Additionally,

participants wanted to compare notes and exchange information about treatments, medication side effects, and outside support networks. The exchange of information helped people feel less alone, and had a problem-solving effect as well. Another topic of interest in the groups was the impact of infertility and infertility treatment on marriages. Overall, the authors of this study felt that the bonds formed among group members were surprisingly strong given the short-term nature of the groups.

The other study (Domar et al., 2000) was designed to determine the efficacy of two different group psychology interventions on viable pregnancy rates in women experiencing infertility of less than two years duration. This study was a prospective, controlled, single-blinded, randomized study conducted at a large tertiary-care teaching hospital. Women (n = 184) who had been trying to achieve a pregnancy for one to two years were randomized into a 10-session cognitive-behavioral group, a standard support group, or a routine care control group. They were followed for one year. Seventy-three women discontinued participation in the study within the first year. There were a total of 47 women in the cognitive-behavioral group, 48 women in the support group, and 25 women in the control group. The main outcome measurement was a viable pregnancy and the researchers found that there was a statistically significant difference between participants in the two intervention groups versus the control group. Women who participated in a group psychological intervention had significantly increased viable pregnancy rates compared to women who did not participate in any psychological intervention. This difference was not due to any group demographic differences, including age and duration of infertility, nor was it because of group differences in medical interventions. Of the disproportionate number of patients who dropped out of

the control group, many left the study specifically to join a clinical mind/body program, a Resolve support group, or other forms of therapy, thus contaminating their control status. The researchers concluded that "group psychological interventions appear to lead to increased pregnancy rates in infertile women" (Domar et al., 2000, p. 805).

Domar, the lead author on the second study, and a practitioner and researcher of mind-body medicine state that to successfully treat women's medical conditions, we must treat women's minds along with their bodies. She believes that by using simple relaxation techniques, infertile women can learn to induce the "relaxation response" which she describes as "a physical state of deep rest that occurs when a person is extremely relaxed." According to Domar & Kelly (2002), the relaxation response counteracts the body's physical and emotional responses to stress, allowing it to return to a calm, relaxed state. When a person elicits the relaxation response, there is a measurable decrease in heart rate, blood pressure, breathing rate, stress hormone levels, and muscle tension. By learning how to elicit this response, women who are experiencing infertility will reduce their levels of depressive symptoms, anxiety, anger, and frustration. This in turn will allow them to relax, transform negative thought patterns, express their emotions and develop social support and begin to regain control of their lives. Although it has yet to be determined, perhaps these same techniques could be applied towards reducing the experience of uncertainty, its associated stress, and the increased risk of adverse perinatal outcomes such as LBW in women who undergo treatment to conceive a pregnancy.

In addition to coping and adaptation, the concept of antecedents and their relationship to uncertainty have great relevance for treating infertility. When caring for patients undergoing infertility treatment, nurses must remember that patients are

experiencing intense uncertainty. This situation creates a continuing need for nurses to provide structure in the form of patient education. The findings from this study are useful to women who conceive a pregnancy after experiencing infertility. Nurses reviewing the current study findings along with other study findings with patients may provide information that can be used by patients and their obstetric care providers to evaluate risk and plan for potential complications. Specifically, nulliparous women with a history of infertility who undergo infertility treatment and conceive a singleton pregnancy may be at increased risk for giving birth to a LBW infant and should be monitored closely during pregnancy for restricted neonatal growth. Preventive measures such as diet therapy and reduction of physical activity could be used to reduce the risk of slowed fetal growth (Luke et al., 2003; Luke et al., 2004). When patients can construct a schema, and work with their healthcare provider to develop a plan of care, their level of uncertainty will be reduced.

Study Limitations and Strengths

Although the study contributes new findings to the field, there are several limitations. First, this study used a retrospective design and included women who underwent fertility treatment before January 1, 1998. There have been changes in the techniques used in treatment since that time, thus limiting the findings related to births that occurred prior to January 1st 1998. Second, all of the study participants were residents of Northern California, limiting the generalizability of the study findings. Thirdly, since our data did not include nutritional status which may affect perinatal outcomes and may differ between the fertility status groups, we could not investigate the

relationship between race, ethnicity and nutritional status and fertility conception status and perinatal outcomes.

The causes of adverse perinatal outcomes following treatment for infertility are multifactorial and inherently complex. Challenges include collecting large samples of women who have undergone infertility treatment, measuring many variables on the sample, and using advanced analytic techniques that include multiple variables. One of the major criticisms of previous studies of outcomes in relation to infertility treatment has been the lack of a proper comparison group. Most studies have compared infertile women who have undergone infertility treatment, such as IVF, with data from national birth registries. It has been argued that, in order to evaluate the effect of infertility on outcomes of PTD and LBW, a comparison group of women with a history of infertility who conceive spontaneously is needed. In this study, valid and reliable information has been collected on health history, fertility conception status, infertility diagnosis, and infertility treatment, along with other potential confounding variables and possible modifying factors that would affect the pregnancy and neonatal outcomes. By collecting comprehensive and complete information on each study participant in each group for a variety of covariates, we were able to look at outcomes controlling for potential condounding variables. .

Conclusion

This was the first study to evaluate the difference between three independent groups of women stratified by fertility conception status. We compared women with a history of infertility who conceived a singleton pregnancy with and without treatment

with fertile women who conceived a singleton pregnancy spontaneously, to determine risk factors for adverse perinatal outcomes. These three different groups allowed us to compare women on both fertility status and treatment status. Women did not differ significantly between the three groups on frequency of PTD; however, the three groups of woman were found to differ on maternal age, parity, and delivery of LBW infants. Although the mechanisms underlying the association remain uncertain, factors associated with LBW in women with a history of infertility were nulliparity and infertility treatment.

The Theory of Uncertainty in illness supports the concept that both infertility and infertility treatment are major stressors that can induce physiologic changes that may disrupt reproductive mechanisms. Nurses who care for women experiencing infertility can teach patients relaxation techniques that may support the relaxation response to counteract the body's physical and emotional responses to stress. Nurses also can review research findings with their patients to provide information to patients who may be at increased risk for adverse perinatal outcomes so that they and their obstetric care providers can create a cognitive schema regarding their pregnancy and plan for potential complications.

There are several public policy implications of this study's findings. First, obstetric health care providers should be made aware that nulliparous women who conceive a pregnancy as a result of infertility treatment in Northern California are at increased risk for delivering a LBW infant, and should be monitored closely during pregnancy for signs of fetal growth restriction. Second, future research should continue to evaluate the health of women with a history of infertility and their treatment conceived children to identify other predictors of adverse perinatal outcomes so that additional steps

may be taken to reduce the probability of delivering a LBW infant by nulliparous women who conceive a singleton pregnancy with the assistance of infertility treatment.

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APPENDIX

Table 1

Frequency Table for Singleton Pregnancies by Fertility Status Group

Health Status Variables

Variable	**Infertile with treatment (2) n=542**	**Infertile without treatment (1) n=441**	**Fertile (0) n=1008**	**Statistical comparison** Chi-square(*df*) *p*-value
Chronic Hypertension				
Yes	530 (1.5%)	3 (.7%)	12 (1.2%)	1.381(2), $p = .50$
No	8 (98.5%)	436 (99.3%)	991 (98.8%)	
Missing	4	2	5	
Diabetes				
Yes	5 (.9%)	5 (1.1%)	4 (.4%)	2.903(2), $p = .23$
No	533 (99.1%)	434 (98.9%)	999 (99.6%)	
Missing	4	2	5	
Heart disease				
Yes	3 (.6%)	3 (.7%)	3 (.3%)	1.170(2), $p = .557$
No	535 (99.4%)	436 (99.3%)	1000 (99.7%)	
Missing	4	2	5	
Obesity				
Yes	31 (5.8%)	10 (2.3%)	43 (4.3%)	7.234 (2), $p = .027$*
No	507 (94.2 %)	429 (97.7%)	960 (95.7%)	
Missing	4	2	5	

Variable	**Infertile with treatment (2) n=542**	**Infertile without treatment (1) n=441**	**Fertile (0) n=1008**	**Statistical comparison** Chi-square(*df*) *p*-value
Obesity Post-hoc pairwise contrasts				
0=1				3.479(1), $p = .068$
0=2				1.665(1), $p = .212$
1<2				7.292(1), $p = .009$*
				F-statistic (*df*), *p*-value
Maternal Age				
N	534	438	997	93.668(2), $p < .0005$*
Range	22.08 - 49.04	22.82 - 46.42	16.36 - 47.42	
Mean (*SD*)	36.344 (4.93)	35.25 (4.74)	32.87 (5.10)	
Maternal Age Post-hoc pairwise contrasts				Mean Difference, *p*-value
0<1				-2.38, $p < .0005$*
0<2				-3.47, $p < .0005$*
1<2				-1.09, $p = .002$*
Body Mass Index				
(BMI)	449	376	837	2.777(2), $p = .06$
N	17.16-52.31	15.06-54.82	15.20-48.10	
Range	24.669 (5.37)	24.888 (5.45)	24.19 (5.0)	
Mean (*SD*)				

*$p < .05$.

Table 1
Frequency Table for Singleton Pregnancies by Fertility Status Group

Index Pregnancy Conditions

Variable	**Infertile with treatment (2) n=542**	**Infertile without treatment (1) n=441**	**Fertile (0) n=1008**	**Statistical comparison** Chi-square(*df*) *p*-value
Nulliparous				
Yes	322 (59.7%)	265 (39.8%)	590 (41.5%)	56.158(2) p<.05*
No	217 (40.3%)	175 (60.2%)	418 (58.5%)	
Missing	3	1	0	
Nulliparity Post-hoc pairwise contrasts				
0=1				.141(1), p = .732
0<2				96.758(1), p < .0005*
1<2				64.393(1), p < .0005*
Nulligravida				
Yes (1)	157 (29%)	85 (19.3%)	226 (22.4%)	14.041(2), p= .001*
No (0)	385 (71%)	356 (80.7%)	782 (77.6%)	
Missing	0	0	0	
Nulligravida Post-hoc pairwise contrasts				
0=1				1.324(1), p = .274
0<2				11.658(1), p =.001*
1<2				13.381(1), p < .0005*

Variable	Infertile with treatment (2) n=542	Infertile without treatment (1) n=441	Fertile (0) n=1008	Statistical comparison Chi-square(*df*) *p*-value
Pregnancy-Induced Hypertension				
Yes	35 (6.8%)	25 (6%)	63 (6.3%)	.293(2), $p = .86$
No	476 (93.2%)	390 (94%)	940 (93.7%)	
Missing	31	26	5	
Gestational Diabetes				
Yes	51 (9.8%)	22 (5.1%)	87 (8.7%)	7.362(2), $p = .025$*
No	472 (90.2%)	407 (94.9%)	916 (91.3%)	
Missing	19	12	5	
Gestational Diabetes Post-hoc pairwise contrasts				
0=1				4.621(1), $p = .031$
0=2				1.438(1), $p = .257$
1<2				8.478(1), $p = .003$*
Excess weight gain				
Yes	2 (.4%)	3 (.7%)	7 (.7%)	.674(2), $p = .714$
No	536 (99.6%)	436 (99.3%)	996 (99.3%)	
Missing	4	2	5	
Smoking				
Yes	9 (1.9%)	8 (2.1%)	65 (6.8%)	24.268(2), $p < .0005$*
No	463 (98.1%)	373 (97.9%)	887 (93.2%)	
Missing	70	60	56	

Variable	Infertile with treatment (2) n=542	Infertile without treatment (1) n=441	Fertile (0) n=1008	Statistical comparison Chi-square(*df*) *p*-value
Smoking Post-hoc pairwise contrasts				
0>1				12.193(1), $p < .0005$*
0>2				27.203(1), $p < .0005$*
1=2				.457(1), $p = .478$
Alcohol				
Yes (1)	35 (7.6%)	50 (13.4%)	113 (12.1%)	8.561(2), $p = .014$*
No (0)	425 (92.4%)	322 (86.6%)	823 (87.9%)	
Missing	82	69	72	
Alcohol Post-hoc pairwise contrasts				
0=1				.908(1), $p = .357$
0>2				14.375(1), $p < .0005$*
1>2				16.327(1), $p < .0005$*
Intra-uterine growth restriction (IUGR)				
Yes	19 (3.5%)	11 (2.5%)	16 (1.6%)	
No	523 (96.5%)	430 (97.5%)	992 (98.4%)	5.831(2), $p = .054$
Missing	0	0	0	

Variable	Infertile with treatment (2) n=542	Infertile without treatment (1) n=441	Fertile (0) n=1008	Statistical comparison Chi-square(*df*) *p*-value
Small for Gestational Age (SGA)				
Yes	14 (2.7%)	9 (2.1%)	11 (1.1%)	5.309(2), $p = .07$
No	505 (97.3%)	420 (97.9%)	976 (98.9%)	
Missing	23	12	21	
Sepsis				
Yes	9 (1.7%)	6 (1.4%)	10 (1%)	1.435(2), $p = .488$
No	510 (98.3%)	423 (98.6%)	977 (99%)	
Missing	23	12	21	
Fetal/ Neonatal Death				
Yes	9 (2%)	4 (1.1%)	7 (.8%)	3.553(2), $p = .169$
No	448 (98%)	374 (98.9%)	862 (99.2%)	
Missing	85	63	139	

*$p < .05$.

Table 1
Frequency Table for Singleton Pregnancies by Fertility Status Group

Perinatal Outcomes

Variable	**Infertile with treatment (2) n=542**	**Infertile without treatment (1) n=441**	**Fertile (0) n=1008**	**Statistical comparison** Chi-square(*df*) *p*-value
LBW (<2500 g)				
Yes (1)	56 (10.8%)	37 (8.6%)	63 (6.4%)	9.120(2), $p = .01$*
No (0)	464 (89.2%)	392 (91.4%)	925 (93.6%)	
Missing	22	12	20	
LBW Post-hoc pairwise contrasts				
0=1				3.555(1), $p = .069$
0<2				101.731(1), $p < .0005$*
1<2				76.534(1), $p < .0005$*
Preterm (<37 weeks)				
Yes (1)	42 (8.1%)	29 (6.8%)	65 (6.6%)	1.229(2), $p = .54$
No (0)	478 (91.9%)	400 (93.2%)	923 (93.4%)	
Missing	22	12	20	

*$p < .05$.

Table 2

Unique Characteristics of the Infertile Cohort

Variable	**Infertile with Treatment N=542**	**Infertile without Treatment N=441**	**Statistical comparison** Chi-square(*df*) *p*-value Odds Ratio (95% CI)
Infertility Diagnoses			
Male factor			
Yes	171 (32.3%)	84 (19.4%)	20.601(1), $p < .0005$*
No	358 (67.7%)	350 (80.6%)	1.99 (1.475 – 2.686)
Missing	13	7	
Ovarian dysfunction			
Yes	354 (66.9%)	239 (55.1%)	14.149(1), $p < .0005$*
No	175 (33.1%)	195 (44.9%)	1.65 (1.27 – 2.145)
Missing	13	7	
Uterine disorders			
Yes	117 (22.1%)	86 (19.8%)	.759(1), $p = .384$
No	412 (77.9%)	348 (80.2%)	.910 (.669 – 1.186)
Missing	13	7	
Tubal or pelvic damage			
Yes	186 (35.2%)	162 (37.3%)	.485(1), $p = .486$
No	343 (64.8%)	272 (62.7%)	1.581 (.98 – 2.55)
Missing	13	7	

Variable	Infertile with Treatment N=542	Infertile without Treatment N=441	Statistical comparison Chi-square(*df*) *p*-value Odds Ratio (95% CI)
Endocrine or hormonal disorders			
Yes	56 (10.6%)	50 (11.5%)	.213(1), $p = .645$
No	473 (89.4%)	384 (88.5%)	1.149 (.840 – 1.571)
Missing	13	7	
Cervical disorders			
Yes	52 (9.8%)	28 (6.5%)	3.572(1), $p = .059$
No	477 (90.2%)	406 (93.5%)	.846 (.481 – 1.487)
Missing	13	7	
Unexplained infertility			
Yes	26 (4.9%)	25 (5.8%)	.340(1), $p = .560$
No	503 (95.1%)	409 (94.2%)	.909 (.607 – 1.362)
Missing	13	7	

*$p < .05$.

Table 3

Unique Characteristics of the Infertile With Treatment Group

Infertility Treatment Type	Infertile with Treatment N=542
Medications	
Yes	407 (76.9%)
No	122 (23.1%)
Missing	13
Intra-Uterine Insemination (IUI)	
Yes	215 (40.6%)
No	314 (59.4%)
Missing	13
In-vitro Fertilization (IVF)	
Yes	64 (12.1%)
No	465 (87.9%)
Missing	13
Intracytoplasmic Sperm Injection (ICSI)	
Yes	24 (4.5%)
No	505 (95.5%)
Missing	13
Fetal Reduction	
Yes	5 (.9)
No	537 (99.1%)
Missing	0

*$p < .05$.

Table 4

Correlations between perinatal outcomes and mother's health and perinatal status

	preterm (<37 weeks)	low birth weight (<1500g)	nulliparous	nulligravida	smoke during pregnancy	alcohol during pregnancy	obesity	mother age	gestational diabetes
preterm (<37 weeks)	1.000	.201(*)	.069(*)	.029	-.016	.014	.022	.023	.013
low birth weight (<1500g)		1.000	.023	.010	-.014	.037	-.017	-.001	-.022
nulliparous			1.000	.601(*)	-.015	.012	-.044	-.121(*)	-.012
nulligravida				1.000	-.065(**)	-.015	-.052(*)	-.187(*)	.001
smoke during pregnancy					1.000	.221(*)	.005	-.034	-.037
alcohol during pregnancy						1.000	-.014	-.005	-.042
obesity							1.000	-.022	.056(*)
mother age								1.000	.024
gestational diabetes									1.000

* Correlation is significant at the 0.05 level (2-tailed).

Table 5

Infertility group as a predictor of low birth weight compared to fertile group controlling for maternal age, nulliparity, obesity, and gestational diabetes

Independent Variables n=1878 (Missing=113)	**Chi-square(*df*), *p*-value**		**-2 Log likelihood**	**% Variance**	**Correctly Classified**
Final Model	14.425(6), .025*		1036.341	.8 – 1.8%	92%
	B	**S.E.**	**Wald(*df*)**	***p*-value**	**Odds Ratio (95% C.I)**
Infertility No Treatment	.26	.225	1.34(1)	.247	1.297 (.835 – 2.015)
Infertility With Treatment	.441	.21	4.417(1)	.036*	1.553 (1.03 – 2.343)
Maternal Age	.011	.017	.425(1)	.515	1.011 (.978 – 1.046)
Nulliparity	.412	.177	5.426(1)	.02*	1.51 (1.068 – 2.137)
Obesity	.146	.409	.128(1)	.72	1.158 (.519 – 2.579)
Gestational Diabetes	-.3	.34	.777(1)	.378	.741 (.380 – 1.444)
Constant	-3.211	.606	28.084(1)	.000	.04

*$p < .05$.

Table 6

Infertility group as a predictor of preterm delivery compared to fertile group controlling for maternal age, nulliparity, obesity, and gestational diabetes

Independent Variables n=1878 (Missing=113)	**Chi-square(*df*), *p*-value**		**-2 Log likelihood**	**% Variance**	**Correctly Classified**
Final Model	11.684(6), .069		954.072	.06 – .15%	92%
	B	**S.E.**	**Wald(*df*)**	***p*-value**	**Odds Ratio (95% C.I)**
Infertility No Treatment	.012	.240	.002(1)	.961	1.012 (.632-1.62)
Infertility With Treatment	.112	.222	.254(1)	.641	1.118 (.724 – 1.728)
Maternal Age	.017	.018	.895(1)	.344	1.017 (.982 – 1.055)
Nulliparity	.546	.188	8.475(1)	.004*	1.727 (1.195– 2.494)
Obesity	.429	.388	.1226(1)	.268	1.536 (.718 – 3.285)
Gestational Diabetes	.136	.307	.196(1)	.658	1.145 (.628 – 2.09)
Constant	-3.513	.641	30.059(1)	.000	.0

*$p < .05$.

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