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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

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## ABSTRACT

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 a fertile woman. Data were collected at eleven infertility clinics in Iraq Using a retrospective cohort design, record review was conducted on women who carried singleton pregnancies to ≥ 20 weeks gestation. These women. were stratified by method of conception: women who conceived using infertility treatment (n=54), women who conceived naturally following a history of infertility (n=44), and fertile women (n= 100). 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 an LBW infant. Women with a history of infertility who had treatment were 1.55 times more likely to have an LBW infant compared to the fertile group controlling for maternal age, nulliparity, gestational diabetes, and obesity.

**KEYWORDS**: Preterm delivery, low birth weight, singleton pregnancies, infertility.

## INTRODUCTION

Infertility is defined as the inability of a couple to achieve conception after one year of unprotected intercourse. Infertility incidence rates range from 10% to 20% of American couples of childbearing age. 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.[1]

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. Most couples expect they will conceive once they decide to have a child. 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 concern about delayed conception has been identified, about half of all-American couples experiencing infertility will pursue medical assessment and treatment.[2]

Evaluation for infertility begins with a sequence of tests for both partners. This may suggest or reveal a cause for infertility. Even after the cause of infertility has been diagnosed, however, there is no guarantee that treatment will be 2 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).[3]

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).[4] 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 spontaneous conception. IVF, an experimental procedure developed in 1978 to treat women with fallopian tube damage, 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.).[5]

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. 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.[6]

The most 3 recent collaborative reports 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, 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.[7]

**BACKGROUND**

Research studies show that there may be an association between treatment for infertility and adverse perinatal outcomes such as low birth weight (LBW) defined as a birth weight 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. LBW is associated with neurological problems such as cerebral palsy, cognitive and neuromotor difficulties, and behavioral problems during childhood.[8] LBW and PTD infants also 4 have been identified as having difficult temperaments. 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.[9] The use of IVF has increased dramatically worldwide since the birth of the first IVF-conceived child in 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.[10] Other treatments for infertility have been much less studied. If an association between treatment

assisted conception and PTD and LBW infants are 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.[11] 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.[12]

**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.[13] 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 multiple births (22.4%) as compared with approximately 1% in the Australian general 7 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 pregnancies.[14]

Researchers in Great Britain described the birth characteristics of children conceived by ART before 1988 and compared them with national perinatal statistics. 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.[15] 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.[16] 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.[17] 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 the 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 9 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 pregnancies. 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 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.[18]

## METHODS

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.

The health status, index pregnancy conditions, and perinatal outcomes of LBW and PTD of fertile women who conceived a singleton pregnancy spontaneously (n =54) women who had a history of infertility who conceived a singleton pregnancy spontaneously (n = 44), and women who had a history of infertility who conceived a singleton pregnancy with treatment (n = 100).

## RESULTS

### 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:** (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:** (41.5%) in the fertile comparison group, (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:** (22.4%) in the fertile comparison group, (19.3%) in the infertile without treatment group, and (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:** (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.

**Gestational Diabetes**: (8.7%) in the fertile comparison group, (5.1%) in the infertile without treatment group, and (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 7 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)**: (6.3%) in the fertile comparison group, (6%) in the infertile without treatment group, and (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):** (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):** (1.1%) in the fertile comparison group, (2.1%) in the infertile without treatment group, and (2.7%) in the infertile with treatment group delivered an 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.

## DISCUSSION

Women who were members of the three groups (fertile comparison, infertile without treatment, and infertile with treatment) were compared on demographic characteristics, chronic health conditions, and index pregnancy conditions. 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 was 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 the 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, null gravity, smoking, and alcohol consumption during the index pregnancy and the development of gestational diabetes during the index pregnancy.[19]

Specifically, the infertile with treatment group were 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 an LBW infant than women in the fertile comparison group; however, there was no difference in the rate of PTD between the three groups.

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 the frequency of PTD; however, the three groups of women 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.[20]

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 an 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 98 may be taken to reduce the probability of delivering an LBW infant by nulliparous women who conceive a singleton pregnancy with the assistance of infertility treatment.

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