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Preterm delivery and low birth weight in singleton pregnancies conceived by women with and without a history of infertility

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Objective: To determine predictors of low birth weight (LBW) and preterm delivery (PTD) in singleton pregnancies conceived by women with and without a history of infertility.

Design: Retrospective cohort study.

Setting: Eleven infertility clinics in northern California.

Patient(s): Three groups of women who carried singleton pregnancies to ≥ 20 weeks' gestation: 542 infertile women who conceived after treatment, 441 infertile women who conceived spontaneously, and 1,008 fertile women for comparison.

Intervention(s): Chart review.

Main Outcome Measure(s): Association of LBW or PTD with infertility treatment, maternal age, parity, obesity, or development of gestational diabetes.

Result(s): Infertile women who conceived with treatment were more likely to be obese, develop gestational diabetes, and have ovarian, ovulatory, or male factor infertility than infertile women who conceived spontaneously. Infertile women who conceived after treatment had 1.61 times greater odds of having an LBW infant. Nulliparity was an independent predictor of LBW and PTD in all three groups after controlling for maternal age, history of infertility, infertility treatment, obesity, and gestational diabetes.

Conclusion(s): Nulliparous women and women with a history of infertility who conceive a singleton after treatment may be at increased odds for having an LBW infant. Infertile women do not appear to be at increased odds for PTD. (Fertil Steril® 2012;98:681–6. ©2012 by American Society for Reproductive Medicine.)

Key Words: Infertility, low birth weight, obstetric, outcomes, perinatal, premature, preterm delivery

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Low birthweight (LBW) and preterm delivery (PTD) are of clinical concern because both are associated with increased risks of neonatal morbidity and mortality as well as

problems during childhood such as cerebral palsy, cognitive and neuromotor difficulties, and behavioral difficulties (1–7). Although an association between LBW (defined as a birthweight

less than 2,500 g) and PTD (defined as delivery before 37 weeks' gestation) (8) has been suggested for in vitro fertilization (IVF) (9), an association with infertility treatments other than assisted reproductive technology (ART) has been much less studied. The goal of this retrospective cohort study is to determine the risk factors for LBW and PTD by comparing three groups of women: [1] infertile women who conceived a singleton pregnancy as a result of infertility treatment, [2] infertile women who conceived a singleton pregnancy spontaneously,

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and [3] women without a history of infertility who conceived spontaneously.

MATERIALS AND METHODS

A cohort of 51,318 women who underwent evaluation or treatment for infertility between 1965 and 1998 at 14 infertility practices in California (11 in northern California and three in southern California) was assembled for the purpose of conducting health outcomes studies. Eligible women were evaluated for infertility or received treatment between January 1, 1965, and January 1, 1998, and did not have a personal history of cancer.

For this study, the cohort was limited to 30,448 women who underwent evaluation or treatment for infertility between January 1, 1990, and January 1, 1998, at 11 northern California infertility practices (six private, one university-affiliated program, and four in the Kaiser Permanente Medical Care Program). These women were linked to the State of California Birth Statistical Master File and the State of California Fetal Death Statistical Master File to identify fetal deaths and births that occurred between January 1, 1994 and January 1, 1998. Through both linkages, 7,402 infertile women who had achieved a pregnancy of ≥ 20 gestational weeks were identified. A random sample of 2,565 women was obtained of which 1,365 were Kaiser members for whom we had institutional review board approval to review their medical records. The remaining women were sent letters by their infertility provider inviting them to participate in the study. The final study population comprised 983 women who gave birth to singletons, met the eligibility criteria, and had complete medical record information. If the woman had more than one eligible pregnancy during the study period, the index pregnancy was randomly selected using a random number generator. Institutional review board approvals were obtained from the Committee on Human Research at the University of California–San Francisco; the Committee for the Protection of Human Subjects of the State of California, and the institutional review board of the Kaiser Foundation Research Institute.

The fertile cohort was determined by identifying pregnancies that lasted to ≥ 20 weeks' gestation in the State of California Birth Statistical Master File and the State of California Fetal Death Statistical Master File. For each woman identified, the next four certificates for women delivering in the same geographic area were reviewed to maximize frequency matches on date of delivery or fetal death (± 2 months), maternal age, and the exact number of gestations. Of this cohort, 2,156 women were sent letters inviting them to participate in the study. Of this group, 1,008 women who gave birth to singletons and met the eligibility criteria agreed to participate. Each participant was asked to release medical record information for herself and her child(ren) and to confirm that she was a resident of northern California at the time of the delivery or resolution of the pregnancy, did not have a history of infertility, did not take longer than 12 months to conceive any pregnancy, did not experience ≥ 3 spontaneous abortions, and did not use infertility services. The study recruitment process is illustrated in Figure 1.

All data in this study came from medical record review (Supplemental Material and Methods, available online).

Infertility diagnoses and diagnostic tests and treatments for infertility were abstracted from medical records using standardized data collection forms. Information was also collected on health status, pregnancy conditions, and perinatal outcomes for all study participants.

To compare outcomes across all three study groups, we used *t*-tests, analysis of variance (ANOVA), and chi-square analyses. $P < .05$ was considered statistically significant. SAS Version 9.2 (SAS Institute) was used to conduct all analyses. Bonferroni post hoc contrasts were conducted on all variables that were statistically significantly different across the three groups. A priori power calculations conducted using the Poisson approximation, with two-sided alpha of 0.05, demonstrated 96% or greater power to detect each possible difference between the infertile and fertile cohorts.

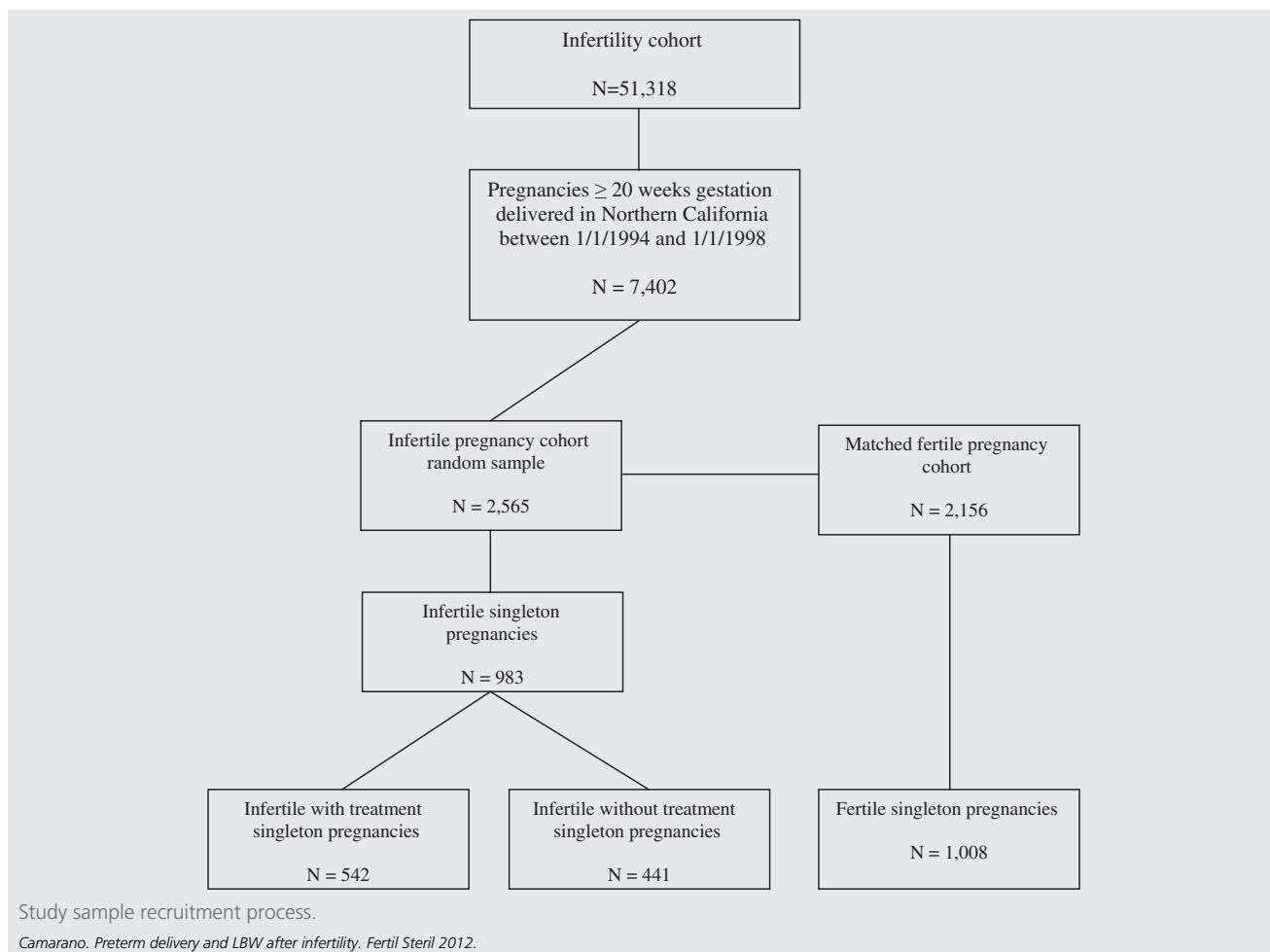
Logistic regression analysis was used to find the best model to describe the relationship between each dependent variable (PTD, LBW) and set of independent variables. To determine potential multicollinearity between independent variables, Spearman rho correlations and variance inflation factors (VIF) were calculated. Variables that were considered for inclusion in the model were those that had associations with PTD or LBW showing $P \leq .05$ in bivariate analyses. Clinically significant variables and potential confounding variables were identified through a review of the literature and included maternal age and nulliparity. These were included in all models as potential confounders or effect modifiers. In an effort to examine the incremental effect of ART, infertility treatment was further modeled by separating ART from non-ART treatment.

RESULTS

Of the 983 women in the infertile cohort, 542 (55%) conceived with cycle-based infertility treatment, and 441 (45%) conceived spontaneously without infertility treatment (i.e., they had not undergone any infertility treatment within two menstrual cycles or 60 days before the estimated day of conception). Of the women who conceived after infertility treatment, 77% conceived using medications to induce or augment ovulation, 41% used intrauterine insemination (IUI), 12% conceived with IVF without intracytoplasmic sperm injection (ICSI), and 5% conceived using IVF with ICSI. The infertility diagnoses are listed in Table 1. Infertile women who conceived with treatment were more likely to have an ovarian or ovulatory dysfunction diagnosis or to have a partner with male factor infertility as compared with infertile women who conceived without treatment. Oocyte donation was used by 22 (2%) of the women in the treatment cohort, and 71 women (7%) used donor sperm.

Women who conceived with treatment were on average 1.1 years older than women who conceived without treatment, and 3.5 years older than the fertile comparison group; they also were more likely to be nulliparous, nulligravid, and at greater risk for obesity and to develop gestational diabetes during the index pregnancy as compared with the other groups. Women in the fertile comparison group were more likely to smoke during the index pregnancy than either infertile group. Both the fertile comparison group and the women who conceived without treatment were more likely

FIGURE 1



to consume alcohol during the index pregnancy when compared with the women who conceived with treatment. However, patients and health-care providers may have under-assessed or underreported consumption of both smoking and alcohol use, as this information was not uniformly noted and/or was missing from a high proportion of the medical records. Because this resulted in a loss of power to evaluate these variables, they were not included in the final model.

Women who conceived with treatment 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. These results are summarized in Table 2.

A logistic regression was performed to determine factors associated with increased odds of having an LBW singleton infant. The model contained seven independent

TABLE 1

Infertility diagnoses for the infertile cohort.				
Infertility diagnosis	Infertile with treatment (n = 542)	Infertile without treatment (n = 441)	P value	Odds ratio (95% CI)
Ovarian dysfunction	354 (66.9)	239 (55.1)	< .0001	1.65 (1.27–2.15)
Male factor	171 (32.3)	84 (19.4)	< .0001	1.99 (1.48–2.69)
Tubal or pelvic damage	186 (35.2)	162 (37.3)	.49	1.58 (0.98–2.55)
Uterine disorders	117 (22.1)	86 (19.8)	.38	0.91 (0.67–1.19)
Endocrine or hormonal disorders	56 (10.6)	50 (11.5)	.65	1.15 (0.84–1.57)
Cervical disorders	52 (9.8)	28 (6.5)	.06	0.85 (0.48–1.49)
Unexplained infertility	26 (4.9)	25 (5.8)	.56	0.91 (0.61–1.36)

Note: Unless stated otherwise values are presented as n (%). Diagnosis categories are not mutually exclusive. CI = confidence interval.

Camarano. Preterm delivery and LBW after infertility. Fertil Steril 2012.

TABLE 2

Characteristics and health status of infertile and fertile women who conceived a singleton pregnancy.

Variable	Infertile with treatment (n = 542)	Infertile without treatment (n = 441)	Fertile (n = 1,008)	P value
Maternal age (y, mean ± SD)	36.34 ± 4.9	35.25 ± 4.7	32.87 ± 5.1	< .0001
BMI (mean ± SD)	24.669 ± 5.4	24.888 ± 5.5	24.19 ± 5.0	.06
Nulliparous	322 (59.7)	265 (39.8)	590 (41.5)	< .0001
Nulligravida	157 (29.0)	85 (19.3)	226 (22.4)	.001
Chronic hypertension	8 (1.5)	3 (0.7)	12 (1.2)	.50
Diabetes before pregnancy	5 (0.9)	5 (1.1)	4 (0.4)	.23
Heart disease before pregnancy	3 (0.6)	3 (0.7)	3 (0.3)	.56
Obesity before pregnancy	31 (5.8)	10 (2.3)	43 (4.3)	.03
Pregnancy-induced hypertension	35 (6.8)	25 (6.0)	63 (6.3)	.86
Gestational diabetes	51 (9.8)	22 (5.1)	87 (8.7)	.03
Excess weight gain during pregnancy	2 (0.4)	3 (0.7)	7 (0.7)	.72
Smoking during pregnancy	9 (1.9)	8 (2.1)	65 (6.8)	< .0001
Alcohol during pregnancy	35 (7.6)	50 (13.4)	113 (12.1)	.01
IUGR	19 (3.5)	11 (2.5)	16 (1.6)	.05
SGA	14 (2.7)	9 (2.1)	11 (1.1)	.07
Sepsis	9 (1.7)	6 (1.4)	10 (1.0)	.49
Fetal or neonatal death	9 (2.0)	4 (1.1)	7 (0.8)	.17
Preterm (<37 wk)	42 (8.1)	29 (6.8)	65 (6.6)	.54
LBW (<2,500 g)	56 (10.8)	37 (8.6)	63 (6.4)	.01

Note: Unless stated otherwise values are presented as n (%). BMI = body mass index; IUGR = intrauterine growth restriction; LBW = low birthweight; SD = standard deviation; SGA = small for gestational age.

Camarano. Preterm delivery and LBW after infertility. *Fertil Steril* 2012.

variables, including maternal age, nulliparity, fertile, infertile conceived with treatment, infertile conceived without treatment, obesity during index pregnancy, and gestational diabetes during index pregnancy. As most studies of LBW in women who have a history of infertility reference nulliparity as a variable, nulliparity was included in this model although nulliparity and nulligravidity were highly correlated ($r = .60$).

The final logistic regression model with LBW as the outcome was statistically significant ($P < .05$), indicating that the model was able to distinguish between women who did and did not give birth to an LBW infant. As shown in Table 3, infertility treatment and nulliparity were independent predictors of LBW. Infertile women who conceived after treatment were at 1.61 (95% CI, 1.08–2.41) odds more likely to give birth to an LBW infant than fertile women, after controlling for maternal age, nulliparity, obesity, and gestational diabetes. Infertile

women who conceived a pregnancy without treatment and fertile women had similar odds of LBW infants ($P = .20$). Nulliparous women were at 1.54 (95% CI, 1.09–2.16) greater odds to give birth to an LBW infant than parous women after controlling for maternal age, infertility treatment, obesity, and gestational diabetes. Although infertility treatment was statistically significantly associated with LBW, conception by ART (odds ratio [OR] 1.6; 95% CI, 1.00–2.55) conferred no additional risk ($P = .88$ for ART vs. non-ART treatment). Additionally, no multicollinearity was seen between nulliparity and treatment; thus, nulliparity appears to be an independent predictor of LBW.

Subsequent mediation analyses were conducted to assess potential causal pathways for each possible mediator. All mediators that were statistically significant in the model were entered together, and the combined effect on the infertility covariate was observed. These analyses found that cervical factors, endometriosis, and uterine anomalies together account for up to 59% of the infertility effect. However, diethylstilbestrol (DES) exposure did not have a mediating affect (see Supplemental Material and Methods).

To test whether women who conceived with donor gametes are at greater risk for LBW as a result of any immunological vulnerability associated with that treatment approach, post hoc analyses were performed to take the use of donor gametes into account. In addition to the base model, we modeled with separate donor sperm and donor oocyte covariates, with a single categorical infertility covariate breaking out the donor oocyte/sperm group, and a subset model excluding those that used donor gametes. In none of the models did the use of donor gametes predict LBW ($P > .05$).

The final model with PTD as the dependent variable was not statistically significant ($P = .07$), indicating that the model

TABLE 3

Predictors of low birthweight infants in study population.

	Odds ratio (95% CI)	P value
Infertile, conception		
With treatment	1.61 (1.08–2.41)	.02
Without treatment	1.33 (0.86–2.06)	.20
Maternal age (y)		
<24	1.06 (0.43–2.61)	.90
30–34	1.30 (0.76–2.19)	.40
35–39	1.25 (0.73–2.15)	.50
≥40	1.06 (0.55–2.014)	.76
Nulliparity	1.54 (1.09–2.16)	.01
Obesity	1.11 (0.50–2.49)	.80
Gestational diabetes	0.72 (0.37–1.41)	.33

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was not able to distinguish between women who did and did not give birth to a PTD infant. The only independent variable that made a unique, statistically significant contribution to the model of PTD was nulliparity. Nulliparous women had 1.72 (95% CI, 1.2–2.5) greater odds of giving birth to a PTD infant, after controlling for maternal age, history of infertility, infertility treatment, obesity, and gestational diabetes, as compared with parous women. Post hoc power calculations indicated an 80% power to detect differences in rates of PTD, intrauterine growth restriction (IUGR), small for gestational age (SGA), sepsis, and fetal or neonatal death of 0.7%, 2.6%, 2.3%, 2.2%, and 2.1%, respectively. Thus, the inability to detect even these small differences may indicate that infertile women were not at increased risk of these adverse outcomes.

DISCUSSION

One of the most significant clinical sequelae of infertility treatment is the high frequency of multiple births and associated poor perinatal outcomes, including PTD and LBW (10, 11). While some studies have described a similar increased risk in singleton pregnancies after ART (9, 12, 13), others have not (14, 15).

By comparing perinatal outcomes between infertile women who conceived with and without a variety of infertility treatments with a comparison group of fertile women, we were able to look at the effects of both infertility and fertility treatment on PTD and LBW. Because known confounders for adverse perinatal outcomes include maternal age, parity, and multiple gestations, we evaluated only singleton gestations and adjusted for both maternal age and parity. Our final logistic regression model found that infertility treatment and nulliparity were the factors most significantly associated with an increase in the odds of infertile women delivering an LBW infant.

Our findings do not suggest that all fertility treatments necessarily place women at greater risk. 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 may be related to the genetic or immunologic competence of gametes. Although it has been reported that exposure to donor gametes may increase the risk of hypertensive disorders in pregnancy (16), we did not find an increased risk for LBW with the use of donor gametes. When addressing the question “Is infertility treatment associated with LBW, or is LBW due to factors that result in infertility?” it is possible that subtle effects expressed at fertilization, nidation, placentation, or gestation may culminate in an LBW child.

We also identified several significant underlying differences between the groups of infertile and fertile women, including maternal age, parity, and obesity. Maternal age has been associated with an increased risk of infertility as well as hypertensive disorders, gestational diabetes, antepartum hemorrhage, and adverse perinatal outcomes (17–24). Yet in ART-conceived singleton pregnancies, Suzuki and Miyake (25) did not find age to be a factor in obstetric outcomes in nulliparous women aged 35 and older with singleton

pregnancies, and Schieve et al. (12) found an elevated LBW risk that was not associated with maternal age. In our study maternal age did not independently predict LBW.

Nulliparity has also been associated with LBW, abnormal labor, dystocia, cesarean delivery, and adverse perinatal outcomes (26–29). Schieve et al. (12) found an elevated LBW risk in ART-conceived singleton infants born at ≥ 37 weeks' gestation that was not explained by parity, but we found that infertile women who underwent treatment to conceive were more likely to be nulliparous than either fertile women or infertile women who conceived without treatment. When nulliparity was added in the final model, it did predict LBW. One explanation may be that nulliparity serves as a marker for the severity of infertility. Although we found that over half of the infertility effect could be accounted for by mediators, there still remains an unexplained effect of infertility with treatment.

Gestational diabetes and obesity are associated with pregnancy loss, preeclampsia, cesarean delivery, and an increased risk of birth defects (20, 30–33). Maman et al. (34) reported that singleton pregnancies conceived by IVF or ovulation induction were at increased risk for maternal gestational diabetes after controlling for maternal age, gestational age, and parity. In our study, the infertile women who conceived with treatment were not only more likely to be obese and to develop gestational diabetes, but also had an increased incidence of ovarian dysfunction, including polycystic ovary syndrome (PCOS). Because obese infertile women are more likely to have PCOS, they are more likely to require treatment to conceive as well as be at increased risk of developing gestational diabetes during their pregnancy.

We acknowledge several limitations in our study, including that all study participants were residents of northern California. Also, the study design was retrospective and non-experimental, and infertility treatments have evolved over time. Nonetheless, the identification of nulliparity and a history of infertility treatment as risk factors for LBW may serve to alert obstetric care providers and prompt future research focusing specifically on the possible mechanisms whereby women undergoing infertility treatment are at risk for adverse perinatal outcomes.

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SUPPLEMENTAL MATERIAL AND METHODS

Medical Record Abstraction of Infertility Diagnoses and Health Conditions

Trained medical record abstractors reviewed all infertility, prenatal, labor and delivery, and postpartum medical records relating to the index pregnancy for the mother, as well as all medical records for the child up to 6 years of age. Infertility diagnoses were identified during the chart review, and they included male, ovulatory/ovarian, uterine, pelvic, endocrine, and cervical factors. More than one diagnosis could be recorded for both the male and female partner. Male factor infertility included azoospermia, oligospermia, asthenospermia, teratospermia, congenital absence of the vas, retrograde ejaculation, varicocele, and/or vasectomy. Ovulatory/ovarian dysfunction included amenorrhea, oligomenorrhea, oligoovulation, hypermenorrhea, menorrhagia, polycystic ovary syndrome, luteal phase defect or deficiency, hypothalamic amenorrhea, exercise-induced amenorrhea, advanced maternal age, premature ovarian failure, elevated follicle-stimulating hormone levels, perimenopause, menopause, diminished ovarian reserve, and/or poor response to gonadotropins. Uterine factors included myomas, adenomyosis, adenomyoma, intrauterine adhesions, Asherman syndrome, in utero diethylstilbestrol (DES) exposure, congenital anomalies (unicornuate, bicornuate, and septate uterus), and endometrial polyps. Pelvic factors 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 disorders included hyperprolactinemia, hyperthyroidism, hypothyroidism, and congenital adrenal hyperplasia. Cervical disorders included history of cone biopsy, incompetent cervix, “hostile cervical mucus,” or poor postcoital test. Women were characterized as having unex-

plained infertility when no known cause for infertility could be detected.

Medical records also were abstracted to obtain information on health status, index pregnancy conditions, and perinatal outcomes for all study participants. Some of the variables included in the health status information were maternal age at the time of the index pregnancy as well as health conditions before the index pregnancy, including body mass index (BMI), history of chronic hypertension, history of type 1 or 2 diabetes, and heart disease with the exception of mitral valve prolapse. Abstracted index pregnancy information included parity, cigarette smoking, alcohol consumption, gestational diabetes, weight gain during the index pregnancy, pregnancy-induced hypertension, intrauterine growth restriction, neonatal sepsis, and fetal or neonatal death. Perinatal outcome information consisted of birthweight, low birthweight, gestational age, preterm delivery, and other health outcomes as noted in the medical record.

Mediation Analysis

Mediation analysis to assess potential causal pathway variables (e.g., outcomes that are the direct result of infertility and that may also increase the risk of LBW) indicated that cervical factors alone produced very little change in the odds ratio (2% reduction). When considering cervical factors and endometriosis, the odds ratio went from 1.33 to 1.21 (35% reduction) for the infertile group who conceived without treatment; however, neither result was statistically significant. When considering cervical factors, endometriosis, and uterine anomalies simultaneously, the odds ratio was 1.27 (19% reduction); however, the result was not statistically significant. When adding diethylstilbestrol (DES) to the model, the odds ratio was 1.27 (an 18% reduction); again, the result was not statistically significant.