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Pregnancy, Birth, and Infant Outcomes by Maternal Fertility Status: The Massachusetts Outcomes Study of Assisted Reproductive Technology

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Abstract

Background—Births to subfertile women, with and without infertility treatment, have been reported to have lower birthweights and shorter gestations, even when limited to singletons. It is unknown whether these decrements are due to parental characteristics or aspects of infertility treatment.

Objective—To evaluate the effect of maternal fertility status on the risk of pregnancy, birth, and infant complications.

Study Design—All singleton live births of ≥22 weeks' gestation and ≥350 grams birthweight to Massachusetts resident women in 2004–10 were linked to hospital discharge and vital records. Women were categorized by their fertility status as in vitro fertilization (IVF), subfertile, or fertile. Women whose births linked to IVF cycles from the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System were classified as IVF. Women with indicators of subfertility but not treated with IVF were classified as subfertile. Women without indicators of subfertility or IVF treatment were classified as fertile. Risks of fifteen adverse outcomes (gestational diabetes, pregnancy hypertension, antenatal bleeding, placental complications (placenta abruptio and placenta previa), prenatal hospitalizations, primary cesarean, very low birthweight (<1,500g), low birthweight (<2,500g), small-for-gestation birthweight (Z-score ≤−1.28), large-for-gestation birthweight (Z-score ≥1.28), very preterm (<32 weeks), preterm (<37 weeks), birth defects,

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neonatal death (0–27 days), and infant death (0–364 days of life) were modeled by fertility status with the fertile group as reference, and the subfertile group as reference, using multivariate log binomial regression and reported as adjusted risk ratios (ARRs) and 95% confidence intervals.

Results—The study population included 459,623 women (441,420 fertile, 8,054 subfertile, and 10,149 IVF). Women in the subfertile and IVF groups were older than their fertile counterparts. Risks for six out of six pregnancy outcomes and six out of nine infant outcomes were increased for the subfertile group, and five out of six pregnancy outcomes and seven out of nine infant outcomes were increased for the IVF group. For four of the six pregnancy outcomes (uterine bleeding, placental complications, prenatal hospitalizations, and primary cesarean) and two of the infant outcomes (low birthweight and preterm) the risk was greater in the IVF group, with non-overlapping confidence intervals to the subfertile group, indicating a substantially higher risk among IVF-treated women. The highest risks for the IVF women were uterine bleeding (ARR 3.80, 95% CI 3.31, 4.36) and placental complications (ARR 2.81, 95% CI 2.57, 3.08), and for IVF infants, very preterm birth (ARR 2.13, 95% CI 1.80, 2.52) and very low birthweight (ARR 2.15, 95% CI 1.80, 2.56). With subfertile women as reference, risks for the IVF group were significantly increased for uterine bleeding, placental complications, prenatal hospitalizations, primary cesarean, low and very low birthweight, and preterm and very preterm birth.

Conclusions—These analyses indicate that, compared to fertile women, subfertile and IVF-treated women tend to be older, have more pre-existing chronic conditions, and are at higher risk for adverse pregnancy outcomes, particularly uterine bleeding and placental complications. The greater risk in IVF-treated women may reflect more severe infertility, more extensive underlying pathology, or other unfavorable factors not measured in this study.

Keywords

adverse pregnancy outcomes; assisted reproductive technology; infertility; subfertility

Introduction

The outcomes of pregnancies to subfertile women, with and without infertility treatment, have been reported to have more complications, lower birthweights, and shorter gestations, even when limited to singleton births (1–8). There is continued scientific debate regarding the role of parental characteristics, including the etiology of the subfertility (9–12), versus the effect of specific infertility treatments (13–23) in suboptimal outcomes in these women. In addition, an acknowledged drawback of prior in vitro fertilization (IVF) research in the United States has been the self-reported nature of the outcomes data, which is typically provided by the patient herself or by her obstetrical provider. This study seeks to overcome these limitations by linking the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS) data to birth certificate and hospital utilization data, as well as accounting for fertility status. This analysis is part of a larger population-based study of IVF in Massachusetts (11, 24–39). The first analysis of perinatal outcomes from the MOSART study was based on singleton and twin births in 2004–08, and examined four adverse outcomes: preterm birth, low birthweight, small for gestational age, and perinatal death (30). In this analysis, based on births in 2004–10, we have increased the sample size by nearly 50% (singleton births from 320,135 to 459,623), expanded the number

of adverse outcomes from four to 15 (six maternal and nine infant), and separated the analysis by plurality, with the results in singletons presented in this paper, and the results for twins (further divided by like gender and unlike gender pairs) in a subsequent paper (40). This analysis was repeated and expanded to clarify associations, and to further identify factors that may be in the pathway between fertility status, treatment, and perinatal outcomes. The objective of this current analysis is to evaluate the effect of maternal fertility status (fertile, subfertile, or IVF) on the pregnancy and birth outcomes in singleton live births.

Materials and Methods

Study Design and Setting

This longitudinal cohort study included all women with singleton live births of ≥22 weeks gestation and ≥350g birthweight in Massachusetts from July 1, 2004 through December 31, 2010. As a project within the Massachusetts Department of Public Health, the Pregnancy to Early Life Longitudinal (PELL) system links records from birth certificates, hospital discharges, and program data from child health and development programs.

Data Sources

The Pregnancy to Early Life Longitudinal (PELL) data system—The PELL system has linked information on more than 99% of all births and fetal deaths in Massachusetts from 1998–2010 to corresponding hospital utilization data (hospital admissions, observational stays, and emergency room visits) for individual women and their children, including 1,004,320 deliveries. The Massachusetts Department of Public Health (MDPH) and the Massachusetts Center for Health Information and Analysis are the custodians of the PELL data system, composed of individual databases linked together by randomly-generated unique IDs for mother and infant.

The Society for Assisted Reproductive Technology Clinic Online Data Reporting System (SART CORS)—The data source for IVF data for this study was the SART CORS, which contains comprehensive data from more than 83% of all clinics performing IVF and more than 91% of all IVF cycles in the United States (41). Data are collected and verified by SART and reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493). SART maintains HIPAA-compliant business associates agreements with reporting clinics. In 2004, following a contract change with CDC, SART gained access to the SART CORS data system for the purposes of conducting research. The national SART CORS database for 2004–10 contains 930,957 IVF treatment cycles. The data in the SART CORS are validated annually (42) with some clinics having on-site visits for chart review based on an algorithm for clinic selection.

Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART)—The Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) project links data from the SART CORS with the PELL data system to evaluate pregnancy and child health outcomes on a population basis. Human subjects approval was

obtained from Boston University, Massachusetts Department of Public Health, Dartmouth College, and Michigan State University. The study also had the approval of the SART Research Committee.

We constructed the MOSART database by linking the SART CORS and PELL data systems for all Massachusetts births to Massachusetts resident women between July 1, 2004 and December 31, 2010. The starting date was chosen based on the availability of SART CORS data (January 1, 2004) to allow us to capture any births associated with IVF and the end date reflected the latest available linked data of the SART CORS to PELL. A deterministic five phase linkage algorithm methodology was implemented (24) using mother's first and last name, mother's date of birth, father's name, race of both parents, date of delivery, and number of babies born per delivery. Linked files were later identified by use of a linkage ID from which identifiers were removed. The linkage rate was 89.7 % overall and 95.0 % for deliveries in which both zip code and clinic were located in Massachusetts. The linkage yielded pregnancies and deliveries identified for this study as the ***IVF group***.

We identified a subfertile group as previously described (26). Briefly, all Massachusetts deliveries were reviewed for the answer to two questions on the Massachusetts birth certificate about use of fertility drugs and assisted reproduction. Those who answered "yes" to either or both of these questions and had not been identified in the SART CORS linkage were included as ***subfertile***. In addition, any woman who at delivery, or in the 5 years previous to delivery, had been hospitalized with a discharge code of female infertility (ICD-9 diagnosis code 628.0, Infertility-Anovulation, 628.2, Infertility-Tubal Origin, 628.3, Infertility-Uterine Origin, 628.8, Female Infertility of other specified origin, 628.9, Female Infertility of unspecified origin or CPT procedural code V230, Pregnancy With Diagnosis of Infertility) was also included as part of the ***subfertile group*** if they were not in the SART CORS linkage. Deliveries not in either the subfertile or IVF groups were listed as ***fertile***.

Variables—Independent variables included parental ages, race and ethnicity, education, and payor status at delivery; parity (nulliparous and parous), smoking, maternal pre-pregnancy medical conditions (chronic hypertension and diabetes mellitus); and repeat cesarean delivery, and infant gender (Table 1). Dependent variables included gestational diabetes, pregnancy hypertension, uterine bleeding, placental complications (abruptio placenta, placenta previa, and vasa previa), prenatal hospitalizations, breech/malpresentation at delivery, cephalopelvic disproportion at delivery, other excessive bleeding at delivery, primary cesarean delivery, very low birthweight (VLBW, <1,500 grams), low birthweight (LBW, <2,500 grams), small-for-gestation birthweight (SGA, Z-score ≤−1.28), large-for-gestation birthweight (LGA, Z-score ≥1.28), very preterm (<32 weeks), preterm (<37 weeks), birth defects, neonatal death (0–27 days), and infant death (0–364 days). We created composite variables for gestational diabetes, diabetes mellitus, chronic and pregnancy hypertension, and placenta previa, abruptio placenta, and vasa previa using data from the birth certificate and hospital discharge delivery records, using ICD-9 648.8 for gestational diabetes, ICD-9 648.0 or 250 for diabetes mellitus, chronic hypertension as ICD-9 401, 402, 403, 404, or 405, pregnancy-related hypertension as ICD-9 642, placenta previa as ICD-9 641.0 or 641.1, abruptio placenta as ICD-9 641.2, and vasa previa as ICD-9 663.5. The variables of uterine bleeding, breech/malpresentation at delivery, cephalopelvic

disproportion at delivery, other excessive bleeding at delivery were derived from birth certificate records in PELL.

Parental Factors—Factors obtained from the birth certificate included parental ages at delivery, race/ethnicity, and education. Parental age was evaluated as a continuous variable. Parental race/ethnicity was categorized as white, black, Asian, Hispanic, and other. Parental education was categorized as ≤high school or GED (General Education Development diploma), some college or Associate degree, or Bachelor degree or graduate school. Payor status at delivery was a composite of the payor source as reported on the birth certificate and the hospital discharge delivery record. In the multivariate analyses, payor status was categorized as private or public (composite measure of public, self-pay, and free care).

Length of Gestation and Prematurity—Length of gestation was calculated by using the birth certificate delivery date minus date of last menstrual period (LMP) corrected for clinical estimate at early ultrasound. Clinical estimate is used to adjudicate any discrepancies. Deliveries prior to 32 weeks gestation were classified as very early preterm, those less than 37 completed weeks gestation were classified as premature, and those which were 37 weeks or greater were classified as term.

Very Low Birthweight, Low Birthweight, and Small-for-Gestational Age Birthweight—Birthweight was obtained from the birth certificate. Birthweights at each gestational age are normally distributed, and a z-score (or standard deviation score) is the deviation of the value for an individual from the mean value of the reference population divided by the standard deviation for the reference population (43). Birthweight z-scores were calculated to evaluate adequacy of weight-for-age using population-based standards, as recommended by Land (44) and modeled as continuous and categorical variables. We generated gender-, race/ethnicity-, and gestation-specific birthweight means and standard deviations using Massachusetts data for all live births from 1998–2010. Infants with birthweight z-scores ≤−1.28 (below the 10^{th} percentile for gestation and gender) were classified as small-for-gestational age and those with birthweigh z-scores ≥1.28 (above the 90^{th} percentile for gestation and gender) were classified as large-for-gestational age. Birthweights less than 1,500 grams were classified as very low birthweight, and less than 2,500 grams were classified as low birthweight.

Birth Defects—The Massachusetts Birth Defects Monitoring Program (BDMP) conducts statewide, population-based active surveillance of birth defects among Massachusetts residents through 1 year of age. The primary focus of the state surveillance system is the identification of major structural birth defects that occur with or without a chromosomal abnormality or other non-chromosomal malformation syndrome. The program's active surveillance system uses multiple sources of ascertainment, including delivery and specialty care hospitals, and birthing centers. Vital records serve as an additional source of information, providing demographic and clinical information on cases, and acting as an additional source of case-finding. Potential birth defect cases, identified through these varied sources, are assigned to medical record abstractors who review maternal and infant medical records. All cases are coded according to the International Classification of Diseases, Ninth

Revision, Clinical Modification, modified British Pediatric Association (ICD-9-CM/BPA) system. Complex cases and cases in which the infant died are reviewed by a clinical geneticist. The birth defects included in the Massachusetts surveillance are ICD-9 CM codes ranging from 740.0 to 759.9 and several other selected codes outside this range for defects such as DiGeorge syndrome, Pierre Robin sequence and amniotic bands. The birth defects included in this analysis have been identified through the BDMP system and linked to each child's birth data.

IVF Factors—For women in the IVF group, the frequency of infertility diagnoses and IVF treatment parameters was summarized from data from the SART CORS (Table 2). Infertility diagnoses included male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal factors, uterine factors, other factors, and unexplained infertility. IVF treatment parameters included oocyte source (autologous, donor), embryo state (fresh, thawed), number of embryos transferred (1, 2, or >2), and number of fetal heartbeats at the six week ultrasound exam (1 or >1).

Statistical Methods—We compared maternal and paternal demographic characteristics, pre-pregnancy diagnoses, and perinatal outcomes across fertility groups (fertile, subfertile, and IVF) using generalized linear regression for continuous variables and χ^2 for categorical variables; (Tables 1 and 3). The association between fertility status and the six adverse pregnancy outcomes were computed as adjusted risk ratios (ARR) and 95% confidence intervals from multivariate log binomial regression models adjusted for parental ages, race and ethnicity, and education; maternal payor status, smoking, pre-existing conditions (diabetes mellitus and chronic hypertension), and parity; the nine infant outcomes were additionally adjusted for infant gender (Table 4). We used generalized estimating equations (GEE) to account for correlated data. The GEE models accounted for correlations between sequential infants born to the same woman during the time period studied, as there were women who had more than one delivery in the MOSART data system. Given that our research emphasis in this observational study is to analytically examine differences in outcomes between fertility groups adjusting for confounding, we applied GEE methodology for our multivariate models but not for our crude analyses. In addition, in instances where the models didn't converge, log-Poisson models were used (45). Models were computed separately using the fertile group as the reference, and the subfertile group as the reference. Results were considered significant with p values <0.05 for bivariate unadjusted analyses, and when the 95% confidence intervals did not include 1 in the multivariate analyses. All analyses were performed using the SAS software, version 9.3 (SAS Institute).

Results

The descriptive statistics of the 459,623 study women by fertility status group are shown in Table 1. The characteristics of the subfertile and IVF groups were very similar, with women and their male partners more likely to be older, white, college educated, and have private insurance than those in the fertile group. Women in the subfertile and IVF groups averaged 5–6 years older than their fertile counterparts, and were five to seven times more likely to be over age 40. Likewise, their male partners also averaged 4–5 years older than partners of fertile women, and were 2–3 times more likely to be over age 40. More than 80% of

subfertile and IVF women and their partners were white, compared to less than 70% in the fertile group. More than 70–75% of subfertile and IVF women and 65–70% of their male partners were college graduates, compared to about 40% of their fertile counterparts. More than 90–95% of subfertile and IVF women had private insurance, compared to less than 60% in the fertile group.

Infertility diagnoses and IVF treatment parameters for the IVF group are shown in Table 2. Male factor was the most common diagnosis, present in 33.5% of IVF pregnancies, followed by unexplained (22.1%), other factors (15.5%), ovulation disorders (13.2%) and tubal factors (13.1%). Autologous oocytes were used in more than 90% of the IVF pregnancies, and fresh embryos were used in more than 86% of the IVF pregnancies. Two embryos were transferred for the majority of pregnancies (56.9%), with single embryo transferred in 18.5% of pregnancies, and more than two embryos transferred in 24.6% of pregnancies. At the six week ultrasound, 92.0% of the IVF pregnancies had one fetal heartbeat, and 7.4% had more than one fetal heartbeat.

The results of the bivariate unadjusted analyses of pregnancy, birth, and infant outcomes by fertility status are shown in Table 3. Women in the subfertile and IVF groups were more likely to have pre-existing chronic conditions (diabetes and chronic hypertension), and to develop gestational diabetes and/or pregnancy hypertension, and to deliver by primary cesarean. Placental complications, including uterine bleeding, abruptio placenta, placenta previa, vasa previa, and other excessive bleeding at delivery was more likely in the subfertile and IVF groups, consistenly highest in the latter, who also had the highest rates of breech or malpresentation. Mean infant birthweights were more than 3,300 grams for all three fertility groups, with the subfertile group averaging 30 grams higher and the IVF group 47 grams lower than the fertile group. The IVF group had the highest rates of low birthweight, very low birthweight, preterm and very preterm. The rates of birth defects were higher in both the subfertile and IVF groups.

The risks of adverse pregnancy, birth, and infant outcomes by maternal fertility status are shown in Tables 4 and 5. With the fertile group as reference, the risks for six out of six pregnancy outcomes and six out of nine infant outcomes were increased for the subfertile group, and five out of six pregnancy outcomes and seven out of nine infant outcomes for the IVF group. For four of the six pregnancy outcomes and two of the nine infant outcomes, the risk was greater in the IVF group, with non-overlapping confidence intervals to the subfertile group, indicating a substantially higher risk among IVF-treated women and their infants. The highest risks for the IVF women were uterine bleeding (ARR 3.80, 95% CI 3.31, 4.36) and placental complications (ARR 2.81, 95% CI 2.57, 3.08).

With the subfertile group as reference, risks for four out of the six pregnancy outcomes were significantly increased for the IVF group, with highest risks for uterine bleeding (ARR 2.28, 95% CI 1.77, 2.93) and placental complications (ARR 1.95, 95% CI 1.67, 2.28). Risks for four out of nine infant outcomes were significantly increased for the IVF group, with ARRs ranging from 1.21–1.26 for low birthweight and preterm, and 1.40–1.44 for very low birthweight and very preterm.

Discussion

These analyses indicate that compared to fertile women, subfertile and IVF-treated women tend to be older, have more pre-existing chronic conditions, and are at higher risk for adverse pregnancy outcomes, particularly uterine bleeding and placental complications. The greater risk in IVF-treated women may reflect more severe infertility, more extensive underlying pathology, or other unfavorable factors not measured in this study. The frequency and magnitude of the risks of adverse outcomes we found in the IVF group are in accord with prior results from clinical studies (1, 6, 7, 10, 12, 21, 46, 47) and meta-analyses (2, 3, 5, 8). These findings also extend the results from the original analysis (30) which limited adverse outcomes to preterm birth, low birthweight, small-for-gestational age, and perinatal death, demonstrating that compared to fertile women, women with subfertility or treated with IVF are at significantly greater risk for gestational diabetes, pregnancy hypertension, uterine bleeding, placental complications, prenatal hospitalizations, primary cesarean delivery, and their infants are at greater risk for very low birthweight, very preterm birth, birth defects, and neonatal death.

This analysis indicated that women with subfertility with and without IVF treatment were more likely to experience uterine bleeding and placental complications, findings in line with prior research (48–50). The risk of abnormal umbilical cord insertions is also substantially increased in the presence of chronic hypertension, asthma, and diabetes, both pre-gestational and gestational (50). Abnormal umbilical cord insertions are associated with impaired placental development and function, and are linked to a constellation of adverse outcomes which were reported in greater frequency in the IVF group in this analysis, including, pregnancy hypertension, uterine bleeding and placental complications, preterm birth, and birth defects. Pregnancies conceived with assisted reproductive technology are at increased risk of both velamentous cord insertion (AOR 2.16, 95% CI 1.94, 2.41) and marginal insertion (AOR 1.43, 95% CI 1.34, 1.53) (50). In a population-based analysis of Norweigan births in 1999–2009, Ebbing et al (50) reported increased risks in singleton pregnancies with velamentous cord insertions and marginal insertions of vaginal bleeding, abruptio placenta and placenta previa, preeclampsia, preterm birth, and congenital anomalies, with statistically significant AORs ranging from 1.51–3.71 for velamentous cord insertions and 1.20–1.82 for marginal cord insertions. The risks for breech or transverse lie presentations were also increased, particularly with velamentous cord insertions (AORs ranging from 1.69–1.93), resulting in greater need for operative delivery (AORs ranging from 1.11–1.80).

The placentas of pregnancies conceived with assisted reproductive technology have been shown to have important differences compared to both spontaneously-conceived pregnancies, and by IVF treatment parameters. These differences have included significantly larger placental weight and higher placental weight/birthweight ratio (51); increased thickness and a higher incidence of hematomas (52, 53), and altered gene expression (54, 55). Nakamura et al (53) reported that the thickness of the Rohr fibrinoid layer and percent loss of decidua were both significantly highest in the hormonal cycles using thawed embryos, with z-scores of both measures positively correlating with the amount of bleeding at delivery.

Risks for abnormal placentation include factors more common among subfertile and infertile women: older maternal age, endometrial damage and uterine scarring, and short interval between prior cesarean delivery and subsequent pregnancy (56). Studies have confirmed a higher frequency of abnormal placentation in pregnancies conceived through both ovulation induction (46) and IVF (46–48). Compared to women without infertility treatment, Shevell et al (48) reported increased risks of placental abruption with ovulation induction (AOR 2.4, 95% CI 1.3, 4.2) and IVF (AOR 2.4, 95% CI 1.1, 5.2), and placenta previa with IVF (AOR 6.0, 95% CI 3.4, 10.7). A case-control analysis of Masschusetts singleton births in 1997–98 by the CDC reported higher relative risks with IVF of uterine bleeding (relative risk, RR 3.2, 95% CI 1.5, 6.8), placental abruption (RR 3.8, 95% CI 1.6, 9.4), and placenta previa (RR 3.8, 95% CI 1.6, 9.4) (57). Among women with consecutive singleton pregnancies conceived spontaneously versus by IVF, Romundstad reported an AOR 2.9, 95% CI 1.4, 6.1 for placenta previa in the IVF pregnancy (49). Ovulation induction has also been reported to be associated with an increase in placental abruption (48). Subfertile and IVF-treated women also have greater risks of severe maternal morbidity, particularly bleeding requiring blood transfusions (36, 58–60). Factors resulting in suboptimal endometrial function may also play an important role in the risk for antepartum bleeding and abnormal placentation (61). Other factors affecting the endometrium and uterine environment may also be associated with adverse outcomes. Both gonadotropin dose and number of oocytes retrieved are associated with reduced live birth rates and decrements in birthweight (62, 63).

Specific infertility diagnoses may also contribute to the increased risk of adverse pregnancy outcomes in both subfertile and IVF-treated groups. Endometriosis is associated with increased risks of antepartum bleeding and placental complications, irrespective of IVF treatment (31, 64). Our prior analyses of IVF pregnancies indicated that among all infertility diagnoses, endometriosis had the highest rates of uterine bleeding (4.8%) and placenta previa (2.4%) (34). In singleton pregnancies, the infertility diagnosis of uterine factor has been associated with increased risks for breech/malpresentation and cesarean delivery (34, 57).

Because their infertility treatment was most likely performed in the outpatient setting, less is known about the subfertile group than the IVF group, which was linked to an infertility treatment database (SART CORS). The subfertile group is probably quite heterogeneous, given that not all of the women underwent treatment. Some women in the subfertile group had only had an infertility diagnosis but no evidence of infertility treatment in the index pregnancy, making it difficult to determine whether it was the underlying infertility or the treatment, or the combination that was associated with compromised outcomes. Planned analyses, linking outpatient insurance claims data, will help clarify these potential associations in the subfertile group.

In counseling women with subfertility, with or without IVF therapy, there are several modifiable factors which can improve treatment and pregnancy outcomes. Although not evaluated in this study because the variables of maternal height and weight were not available, attainment of body weight within a normal range for height is associated with more successful IVF treatments as well as fewer placental and pregnancy complications (65–73). Second, maintenance of normal blood glucose levels is associated with better

infertility treatment outcomes, as well as lower pregnancy complications and risk of birth defects (74–79). Third, supplementation with folate and multivitamin is reported to be associated with a better IVF treatment outcomes, as well as significantly lower risks of marginal cord insertions, birth defects, and prematurity (80–84). Fourth, attainment of plurality-specific gestational weight gain, with a nutritionally-balanced diet, is associated with better perinatal results (85–87). Other factors, not available in the datasets used in this study, such as stress and occupational fatigue, may also adversely affect infertility therapy and the course and outcome of pregnancy, and should be evaluated during treatment (88–91).

Pregnancy complications may have long-term deleterious effects on women's health, including increased risks for hypertension, diabetes, and cardiovascular disease (92–102), which may be even greater in women with chronic conditions before pregnancy, including infertility. Although studies indicate that the short-term health of children born from infertility treatment is positive, there is limited long-term follow-up data (103–105). The health effects of adverse perinatal outcomes, particularly among those who were conceived with assisted reproductive technology, is an area in need of continued surveillance and research (106, 107).

Strengths and Limitations

The MOSART study, which includes linking IVF cycles to vital records and hospital utilization data, represents the first time these datasets have been linked using direct identifiers from both datasets. IVF national surveillance summaries are limited to birth outcomes reported by the patient herself or her obstetric provider (42, 108–110). Prior studies (108, 109) have relied on linkages between IVF cycles and vital records using only maternal and infant dates of birth, or probabilistic algorithms (42, 110). Although there is a high degree of comparability between the SART CORS and vital records (38), our study design assures more accurate linkage between IVF treatment cycles, vital records, and the hospital discharge data, and a more complete picture of perinatal outcomes. Although this study has several unique advantages over prior IVF research, it is also subject to several limitations. The use of registry data carries the potential risk of misclassification and selection bias. However, the SART CORS variables undergo annual validation (42), and we have additionally validated the SART CORS variables with the MOSART study (38). This study uses retrospective data from several centralized datasets and although this is advantageous to achieve large numbers, we had the disadvantage that data entered into the SART CORS system is not as rigorously controlled as data collected for a prospective research study. Likewise, the primary purpose of vital records is civil registration, with public health research and surveillance being secondary uses. One of the limitations of comparing our results to the published literature is that the latter is often based on data spanning decades, during which time both IVF procedures and outcomes have improved. Another limitation of this analysis is that it only includes women in Massachusetts, and the maternal variables of height and weight were only added to the Massachusetts birth certificate in 2011, and therefore could not be included in this analysis. In addition, the Massachusetts birthweight reference used to calculate birthweight z-scores was based on all Massachusetts live births between 1998–2008, including singletons and multiples, which

may have under-estimated small-for-gestational age outcomes. There may be significant demographic and outcome differences in patient populations in other regions of the country and with other healthcare systems, potentially limiting the generalizability of our findings.

Lastly, because infertility is essentially treated entirely in the outpatient setting, we have likely greatly underestimated the extent of the subfertile group. Although defining and identifying a subfertile population in our MOSART project has been a major step forward, it was deficient in two key areas: 1) the majority of women with subfertility are treated in the outpatient setting, and were therefore not identified by our original methods (which were based on available databases); and 2) we had only limited information on whether births to these subfertile women were spontaneously-conceived or the result of non-ART treatments (i.e., gonadotropin stimulation or intrauterine insemination). In our current analyses, we will be linking to the Massachusetts All Payors Claims Database (APCD) to overcome these two deficiencies. Using APCD outpatient data, we will be able to identify an estimated four-fold more women who have received a diagnosis of subfertility during one or more office visits (ICD codes of the 628 series). We have calculated this increase based on the National Survey of Family Growth's estimate of fertility treatments (3.1% ART, 20.0% ovulation stimulation, and 7.4% IUI) and treatment success (49%,15%, and 20%, respectively) (111). We will also be able to identify specific subfertility-related diagnoses, [endometriosis (ICD 617 series) and ovulatory disorders (ICD 614 series)], fertility medications (Clomiphene citrate, and gonadotropins), and non-ART treatments (intrauterine insemination and donor insemination, CPT codes 58322, 58321). This research is currently underway.

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Condensation

Subfertile and IVF-treated women and their infants are at higher risk for adverse pregnancy and perinatal outcomes, particularly uterine bleeding and placental complications.

Table 1

Maternal and Paternal Demographic Characteristics by Maternal Fertility Group

		All	Fertile	Subfertile	IVF
	N, pregnancies	**459,623**	**441,420**	**8,054**	**10,149**
Maternal	Mean (SD)	29.5 (6.1)	29.3 (6.1)	34.8 (4.6)	35.9 (4.6)
Age (years)	(%) <35	77.7	79.2	45.4	39.1
	35–37	13.0	12.5	26.2	24.9
	38–40	6.7	6.1	18.3	20.4
	41–42	1.8	1.5	6.7	8.7
	≥43	0.8	0.7	3.4	6.9
Paternal	Mean (SD)	32.5 (6.8)	32.3 (6.7)	36.9 (5.5)	37.9 (5.8)
Age (years)	(%) <35	62.5	63.9	33.5	29.0
	35–37	16.0	15.6	24.2	23.2
	38–40	10.5	10.1	20.0	19.9
	41–42	4.3	4.0	8.5	9.4
	≥43	6.8	6.4	13.8	18.7
Maternal Race	Hispanic	14.5	14.9	4.5	3.4
& Ethnicity (%)	White	67.0	66.3	84.3	85.0
	Black	8.7	9.0	3.2	3.2
	Asian	7.7	7.7	6.9	7.4
	Other	2.1	2.2	1.1	1.0
Paternal Race	Hispanic	14.0	14.4	4.3	3.0
& Ethnicity (%)	White	68.0	67.2	85.3	86.6
	Black	8.9	9.1	3.6	3.4
	Asian	7.2	7.3	6.1	6.1
	Other	2.0	2.0	0.9	0.9
Maternal	<HS or HS/GED	36.7	37.8	11.9	9.4
Education (%) *	Some Coll.	21.3	21.5	17.7	15.4
	BS or Graduate	42.0	40.7	70.4	75.3

		All	Fertile	Subfertile	IVF
	N, pregnancies	**459,623**	**441,420**	**8,054**	**10,149**
Patemal	<HS or HS/GED	41.3	42.4	19.6	16.1
Education (%) *	Some Coll.	17.3	17.4	15.1	13.8
	BS or Graduate	41.4	40.2	65.3	70.1
Matemal	Yes	7.3	7.6	1.8	0.7
Smoking (%)	No	92.7	92.4	98.2	99.3
Payor	Private	58.3	56.8	90.0	95.1
Source (%)	Public	40.3	41.7	8.3	3.1
	Self-pay or Free	1.5	1.5	1.6	1.7

*< High School or High School/GED; Some College or Associate Degree; Bachelor Degree or Post-Graduate

All comparisons across fertility groups were significant at p<0.0001

Table 2

Infertility Diagnoses and IVF Treatment Parameters For Women in the IVF Group

Group		**IVF**
N, pregnancies		**10,149**
Factor	Categories	%
Prior IVF cycles		55.2
Mean (SD)		1.4 (1.8)
Infertility	Male Factor	33.5
Diagnoses	Endometriosis	7.8
	Ovulation Disorders	13.2
	Diminished Ovarian Reserve	11.3
	Tubal factors	13.1
	Uterine factors	2.8
	Other factors	15.5
	Unexplained	22.1
Oocyte source	Donor	9.4
	Autologous	90.6
Embryo state	Thawed	13.9
	Fresh	86.1
Embryos	1	18.5
Transferred	2	56.9
	>2	24.6
Fetal heartbeats	1	92.0
At six weeks	>1	7.4

Table 3

Pregnancy, Birth, and Infant Outcomes by Maternal Fertility Group and Plurality at Birth

		All	Fertile	Subfertile	IVF
	N, pregnancies	**459,623**	**441,420**	**8,054**	**10,149**
Pre-existing	Diabetes (%)	1.2	1.2	1.7	2.1
Conditions	Chronic hypertension (%)	1.7	1.7	2.6	3.1
Parity	Nulliparous (%)	45.1	45.8	37.9	62.5
Pregnancy	Gestational diabetes (%)	5.7	5.6	8.5	8.2
Conditions	Pregnancy hypertension (%)	8.7	8.6	10.2	12.6
	Prenatal hospitalization (%)	4.0	4.0	3.9	5.3
	Uterine bleeding (%)	0.7	0.6	1.0	2.6
Labor and	Breech/Malpresentation (%)	4.0	3.9	4.3	7.0
Delivery	Cephalopelvic Disproportion (%)	2.5	2.5	2.6	3.2
Factors	Abruptio placenta (%)	1.2	1.2	1.3	2.1
	Placenta previa (%)	0.7	0.6	1.5	3.3
	Vasa previa (%)	0.03	0.03	0.05	0.27
	Other excessive bleeding (%)	0.7	0.7	0.8	1.5
	Placental complications[1] (%)	1.8	1.7	2.7	5.4
Mode of	Vaginal[2] (%)	68.9	69.5	57.2	54.2
Delivery	Primary cesarean (%)	18.4	18.0	20.5	32.2
	Primary cesarean among nulliparas (%)	31.7	30.8	44.2	50.1
	Repeat cesarean (%)	12.7	12.5	22.3	13.6
Birthweight	Mean grams (SD)	3,359 (552)	3,360 (550)	3,390 (573)	3,313 ± 600
	Very low birthweight (<1,500g, %)	0.8	0.8	0.9	1.5
	Low birthweight (<2,500g, %)	5.4	5.4	5.7	7.7
	Small-for-gestation (Zscore <−1.28, %)	7.9	8.0	6.4	7.8
	Large-for-gestation (Z-score >1.28, %)	9.6	9.5	11.4	9.4
Gestation	Mean weeks (SD)	39.0 (1.8)	39.0 (1.8)	38.7 (1.9)	38.6 ± 2.2
	Early Preterm (<32 weeks, %)	0.9	0.9	1.0	1.6

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		All	Fertile	Subfertile	IVF
	N, pregnancies	**459,623**	**441,420**	**8,054**	**10,149**
	Preterm (<37 weeks, %)	6.4	6.3	7.7	10.3
Birth Defects	Birth Defects (%)	1.64	1.63	2.05	2.10
Gender	Male (%)	51.2	51.2	51.2	51.3
Infant	Infant (0–364 days, %)	0.30	0.30	0.29	0.34
Deaths	Neonatal (0–27 days, %)	0.19	0.19	0.24	0.28
	Postneonatal (28–364 days, %)	0.11	0.12	0.05	0.06

[1]Placental complications include abruptio placenta, placenta previa, and vasa previa

[2]Vaginal includes VBAC, forceps, and vacuum deliveries

All comparisons across fertility groups were significant at p<0.0001, except for the three infant death outcomes, which were not significant

Table 4

Risks of Adverse Pregnancy and Birth Outcomes by Maternal Fertility Status

		Fertility		Fertile Reference		Subfertile Reference	
	Outcome	**Group**	**%**	**ARR**	**95% CI**	**ARR**	**95% CI**
Pregnancy	Gestational	Fertile	5.6	1.00	Reference	0.63	0.42, 0.93
Outcomes[1]	Diabetes[2]	Subfertile	8.5	**1.60**	**1.08, 2.36**	1.00	Reference
		IVF	8.2	1.41	0.85, 2.34	0.89	0.72, 1.09
	Pregnancy	Fertile	8.6	1.00	Reference	0.89	0.83, 0.96
	Hypertension[3]	Subfertile	10.2	**1.12**	**1.05, 1.20**	1.00	Reference
		IVF	12.6	**1.22**	**1.15, 1.28**	1.08	1.00, 1.18
	Uterine	Fertile	0.6	1.00	Reference	0.60	0.48, 0.75
	Bleeding	Subfertile	1.0	**1.67**	**1.33, 2.09**	1.00	Reference
		IVF	2.6	**3.80**	**3.31, 4.36**	**2.28**	**1.77, 2.93**
	Placental	Fertile	1.7	1.00	Reference	0.69	0.60, 0.80
	Complications	Subfertile	2.7	**1.44**	**1.26, 1.66**	1.00	Reference
		IVF	5.2	**2.81**	**2.57, 3.08**	**1.95**	**1.67, 2.28**
	Prenatal	Fertile	4.0	1.00	Reference	0.79	0.70, 0.88
	Hospitalizations	Subfertile	3.9	**1.27**	**1.13, 1.42**	1.00	Reference
		IVF	5.3	**1.81**	**1.65, 1.97**	**1.42**	**1.24, 1.64**
	Primary	Fertile	18.0	1.00	Reference	0.91	0.88, 0.95
	Cesarean[4]	Subfertile	20.5	**1.09**	**1.05, 1.14**	1.00	Reference
		IVF	32.2	**1.20**	**1.17, 1.24**	**1.10**	**1.05, 1.15**
	Primary	Fertile	30.6	1.00	Reference	0.88	0.84, 0.92
	Cesarean (nulliparas)[5]	Subfertile	42.5	**1.14**	**1.09, 1.19**	1.00	Reference
		IVF	44.9	**1.17**	**1.12, 1.22**	1.03	0.97, 1.08

[1]Models adjusted for parental ages, race/ethnicity, education, and payor status; smoking, maternal pre-existing conditions (diabetes mellitus and chronic hypertension), parity.

[2]Models for gestational diabetes adjusted for all factors in model 1 except diabetes mellitus.

[3]Models for pregnancy hypertension adjusted for all factors in model 1 except chronic hypertension.

[4] Models adjusted for parental ages, race/ethnicity, education, and payor status; smoking, maternal pre-existing conditions (diabetes mellitus and chronic hypertension), parity, and breech/malpresentation, cephalopelvic disproportion.

[5] Model adjusted for all factors in model 4 except parity. Bolded values indicate ARRs and 95% CIs which are significantly greater than the reference group.

Table 5

Risks of Adverse Infant Outcomes by Maternal Fertility Status

		Fertility		Fertile Reference		Subfertile Reference	
	Outcome	**Group**	**%**	**ARR**	**95% CI**	**ARR**	**95% CI**
Infant	Very Low Birthweight	Fertile	0.8	1.00	Reference	0.65	0.52, 0.83
Outcomes[1]	(<1,500g)	Subfertile	0.9	**1.53**	**1.21, 1.94**	1.00	Reference
		IVF	1.5	**2.15**	**1.80, 2.56**	**1.40**	**1.06, 1.86**
	Low Birthweight	Fertile	5.4	1.00	Reference	0.74	0.67, 0.81
	(<2,500g)	Subfertile	5.7	**1.36**	**1.24, 1.49**	1.00	Reference
		IVF	7.7	**1.65**	**1.53, 1.78**	**1.21**	**1.08, 1.36**
	Small for	Fertile	8.0	1.00	Reference	1.03	0.94, 1.12
	Gestational Age	Subfertile	6.4	0.97	0.89, 1.06	1.00	Reference
		IVF	7.8	1.04	0.97, 1.12	1.07	0.96, 1.19
	Large for	Fertile	9.5	1.00	Reference	0.96	0.90, 1.03
	Gestational Age	Subfertile	11.4	1.04	0.97, 1.11	1.00	Reference
		IVF	9.4	0.91	0.78, 1.06	0.88	0.74, 1.04
	Very Premature	Fertile	0.9	1.00	Reference	0.68	0.54, 0.85
	(<32 weeks)	Subfertile	1.0	**1.48**	**1.18, 1.85**	1.00	Reference
		IVF	1.6	**2.13**	**1.80, 2.52**	**1.44**	**1.10, 1.89**
	Premature	Fertile	6.3	1.00	Reference	0.74	0.68, 0.80
	(<37 weeks)	Subfertile	7.7	**1.35**	**1.25, 1.47**	1.00	Reference
		IVF	10.3	**1.70**	**1.60, 1.81**	**1.26**	**1.14, 1.39**
	Birth Defects	Fertile	1.6	1.00	Reference	0.82	0.70, 0.97
		Subfertile	2.1	**1.21**	**1.03, 1.42**	1.00	Reference
		IVF	2.1	**1.25**	**1.09, 1.44**	1.03	0.84, 1.27
	Neonatal Death	Fertile	0.19	1.00	Reference	0.54	0.34, 0.86
	(0–27 days)	Subfertile	0.24	**1.85**	**1.16, 2.95**	1.00	Reference
		IVF	0.28	**1.67**	**1.09, 2.56**	0.90	0.49, 1.66
	Infant Death	Fertile	0.30	1.00	Reference	0.66	0.43, 1.01

		Fertility		Fertile Reference		Subfertile Reference	
	Outcome	**Group**	**%**	**ARR**	**95% CI**	**ARR**	**95% CI**
		Subfertile	0.29	1.51	0.99, 2.31	1.00	Reference
		IVF	0.34	**1.51**	**1.04, 2.21**	1.00	0.58, 1.73

[1]Models adjusted for parental ages, race/ethnicity, education, and payor status; smoking, maternal pre-existing conditions (diabetes mellitus and chronic hypertension), parity, and infant gender. Bolded values indicate ARRs and 95% CIs which are significantly greater than the reference group.