HHS Public Access

Author manuscript

Am J Obstet Gynecol. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Am J Obstet Gynecol. 2017 September ; 217(3): 330.e1–330.e15. doi:10.1016/j.ajog.2017.04.025.

Adverse pregnancy, birth, and infant outcomes in twins: Effects of maternal fertility status and infant gender combinations The Massachusetts Outcomes Study of Assisted Reproductive Technology

Barbara Luke, ScD, MPH[1], **Daksha Gopal, MPH**[2], **Howard Cabral, PhD**[2], **Judy E. Stern, PhD**[3], and **Hafsatou Diop, MD, MPH**[4]

[1]Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine, Michigan State University, East Lansing, MI

[2]Department of Biostatistics, Boston University School of Public Health, Boston, MA

[3]Dept of Obstetrics & Gynecology, Geisel School of Medicine at Dartmouth, Lebanon, NH

[4]Massachusetts Department of Public Health, Boston, MA

Abstract

Background—It is unknown whether the risk of adverse outcomes in twin pregnancies among subfertile women, conceived with and without in vitro fertilization (IVF), differ from those conceived spontaneously.

Objective—To evaluate the effects of fertility status on adverse perinatal outcomes in twin pregnancies on a population basis.

Study Design—All twin live births of ≥22 weeks' gestation and ≥350 grams birthweight to Massachusetts resident women in 2004–10 were linked to hospital discharge records, vital records, and IVF cycles. Women were categorized by their fertility status as in vitro fertilization (IVF), subfertile, or fertile, and by twin pair genders (all, like, unlike). Women whose births linked to IVF cycles were classified as IVF; those with indicators of subfertility but without IVF treatment were classified as subfertile; all others were classified as fertile. Risks of six adverse pregnancy outcomes (gestational diabetes, pregnancy hypertension, uterine bleeding, placental complications (placenta abruptio, placenta previa, and vasa previa), prenatal hospitalizations, primary cesarean), and nine adverse infant outcomes (very low birthweight, low birthweight, small-for-gestation birthweight, large-for-gestation birthweight, very preterm (<32 weeks), preterm, birth defects,

Corresponding Author: Barbara Luke, ScD, MPH, Dept. OB/GYN & Reproductive Biology, Michigan State University, 965 Fee Road, East Fee Hall, Room 628, East Lansing, Michigan 48824, 517-353-1678, 517-353-1663-fax, lukeb@msu.edu.

Presented at the 37th Annual meeting, Society for Maternal-Fetal Medicine, Las Vegas, Nevada, January 23–28, 2017

Barbara Luke is a research consultant to the Society for Assisted Reproductive Technology; all other authors report no conflict of interest.

neonatal death, and infant death) were modeled by fertility status with the fertile group as reference, using multivariate log binomial regression and reported as adjusted relative risk ratios (ARRs) and 95% confidence intervals (CI).

Results—The study population included 10,352 women with twin pregnancies (6,090 fertile, 724 subfertile, and 3,538 IVF). Among all twins, the risks for all six adverse pregnancy outcomes were significantly increased for the subfertile and IVF groups, with highest risks for uterine bleeding (ARR 1.92, 2.58, respectively), and placental complications (ARR 2.07and 1.83, respectively). Among all twins, the risks for those born to subfertile women were significantly increased for very preterm birth, and neonatal and infant death (ARR 1.36, 1.89, and 1.87, respectively); risks were significantly increased among IVF twins for very preterm birth, preterm birth, and birth defects (ARR 1.28, 1.07, and 1.26, respectively).

Conclusions—Risks of all maternal and most infant adverse outcomes are increased for subfertile and IVF twins. Among all twins, the highest risks were for uterine bleeding and placental complications for the subfertile and IVF groups, and neonatal and infant death in the subfertile group. These findings provide further evidence supporting single embryo transfer and more cautious use of ovulation induction.

Keywords

adverse pregnancy outcomes; assisted reproductive technology; infertility; like gender twins; subfertility; unlike gender twins

Introduction

In 2015, there were 133,155 twins born in the United States, accounting for 3.3% of all live births (1). The twin birth rate in 2015 was 33.5 twins per 1,000 births, a decline from 2014, when the twin birth rate was 33.9, the highest ever reported. It has long been known that iatrogenic multiple births are the most significant complication of assisted conception (2–4). It is estimated that assisted conception accounts for about 40% of twin births (19% from in vitro fertilization (IVF) and 21% from non-IVF assisted conception) and 77% of triplet and higher-order births (25% from IVF and 52% from non-IVF assisted conception) (5, 6). Internationally, there is a wide range in the twin delivery rate with IVF using fresh or frozen embryos, respectively, ranging from 5.8% and 4.7% in Sweden to 23.6% and 16.0% in Spain, 27.0% and 35.8% in Greece, 28.6% and 15.0% in Germany, and 35.8% and 21.3% in Bulgaria in 2011 (7). In comparison, the twin delivery rate in the United States from IVF during this same time period ranged from 34.9% (for fresh cycles using donor oocytes) to 21.6% (for thawed embryos) (8).

Pregnancies to subfertile women, with and without infertility treatment, have been reported to have more complications, lower birthweights, and shorter gestations, even when adjusted for plurality (9–12). There is continued scientific debate regarding the role of parental characteristics, including the etiology of the subfertility (13–16), versus the effect of specific infertility treatments (17–21) in the 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 (15, 22–38). In this analysis, we have increased the sample size, expanded the number of adverse outcomes, and further divided the twin group by like gender and unlike gender pairs from the original analysis, based on 2004–08 births, with four adverse outcomes (28). 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 twin live births.

Materials and Methods

We used similar methods to that described in the singleton analysis using this same study population (38). The study design and setting, data sources, variables, and statistical analysis are similar, except for the additional provisions made for categorizing and analyzing twin pregnancies and twin infant pairs.

Study Design and Setting

This longitudinal cohort study included all women with twin live births (both liveborn) of ≥22 weeks gestation and both twins ≥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, birth defects registry, 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 (39). 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 (40) 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 (22) 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 deliveries identified for this study as ***IVF deliveries***.

We identified a subfertile group as previously described (24). 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 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 ART groups were listed as ***fertile***. In addition, twin pregnancies were classified by the genders of the twin pair as all twins, unlike genders (male and female), or like genders (both male or both female).

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, or 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 (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 placental complications (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 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. 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 (41). Birthweight z-scores were calculated to evaluate adequacy of weight-for-age using population-based standards, as recommended by Land (42) 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 (SGA) and infants with birthweight z-scores ≥1.28 (above the 90^{th} percentile for gestation and gender) were classified as large-for-gestation (LGA). Birthweights less than 1,500 grams were classified as very low birthweight (VLBW), and less than 2,500 grams were classified as low birthweight (LBW).

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 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 and nine adverse infant outcomes were computed as adjusted relative risk ratios and 95% confidence intervals from multivariate log binomial regression models adjusted for parental ages, race and ethnicity, and education; maternal payor status, pre-existing conditions (diabetes mellitus and chronic hypertension), and parity (Table 4). In a few instances where the models didn't converge, log-Poisson models were used (43). Our statistical models were computed using generalized estimating equations (GEE) in order to account for the correlation resulting from the inclusion of outcomes for each twin. Due to the small sample size within twins (and clustered data), and rare occurence of outcome (death), we decided to remove the covariates that resulted in the least change in the strength of association between fertility status and neonatal and infant death. Chronic diabetes was the least significant

covariate for deaths and when we tested for the effect of association by introducing potential confounders one at a time, chronic diabetes did not alter the risk ratios of either of the fertility group variables by 10% or more, and therefore was not retained in the model. Models were computed separately using the fertile group as the reference, and the subfertile group as the reference, for all twins, and for unlike gender pairs and like gender pairs. 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 10,352 study women by fertility status and twin pair gender 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 4–5 years older than their fertile counterparts, and were about six times more likely to be over age 40. Likewise, their male partners also averaged 3–4 years older than partners of fertile women, and were about twice as likely to be over age 40. More than 80% of subfertile and IVF women and their partners were white, compared to about 70% in the fertile group. More than 70–75% of subfertile and IVF women and about 70% of their male partners were college graduates, compared to about 40–45% of their fertile counterparts. More than 90–95% of subfertile and IVF women had private insurance, compared to about 60% in the fertile group.

The IVF treatment parameters by twin gender groups are shown in Table 2. Autologous oocytes were used in 88% of pregnancies, and fresh embryos in 90%, with no difference by gender pair group. Like gender twins were significantly more often the result of a single embryo transferred (1.9% versus 0.2%, p<0.0001). Both gender groups of IVF pregnancies included about 5% of pregnancies with more than two fetal heartbeats at the six week ultrasound, indicating comparable levels of fetal loss.The distribution of infertility diagnoses did not differ by twin gender group; the most frequent diagnoses were male factor (32.1%), and unexplained (23.7%).

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 be nulliparous, have pre-existing chronic conditions (diabetes and chronic hypertension), 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 were more likely in the subfertile and IVF groups. Breech or malpresentation was most likely in the IVF group: 34.0% for all twins, and highest (35.7%) among unlike gender twins. Primary cesarean delivery was greater than 60% in both subfertile and IVF groups, compared to less than 53% in the fertile group, and was highest (66.7%) among IVF unlike gender twins. The infant outcomes of very low birthweight, low birthweight, and small-for-gestation were highest in the fertile group of like gender twins and the subfertile group of unlike gender twins. Mean length of gestation was about 35 weeks for all groups, with comparable rates of early

preterm and preterm births. The rate of birth defects was about 2%, with slighter higher rates for the IVF group in both like gender (2.59%) and unlike gender twin groups (2.79%). Neonatal and infant mortality were higher among the subfertile group (1.93% and 2.07%, respectively for all twins), and highest among like gender (2.30% and 2.30%) compared to unlike gender twins (1.81% and 1.51%, respectively).

The risks of adverse pregnancy, birth, and infant outcomes by maternal fertility status and infant gender pair groups with the fertile group as reference are shown in Table 4. Among all twins, the subfertile group had the highest rates of adverse outcomes, 67% (10 out of 15) compared to 20% (3 out of 15) in the IVF group, and 13% (2 out of 15) in the fertile group. Among like gender twins, the proportion of the highest rates were equally divided between the subfertile and IVF group, each with 40% (6 out of 15), compared to 20% (3 out of 15) for the fertile group. Among unlike gender twins, 73% (11 out of 15) of the highest rates of adverse outcomes were in the subfertile group, compared to 27% (4 out of 15) in the IVF group, and none in the fertile group. Among all twins, the risks for all six pregnancy outcomes were significantly increased for the subfertile and IVF groups, with highest risks for uterine bleeding (ARRs of 1.92 and 2.58, respectively), and placental complications (ARRs of 2.07 and 1.83, respectively); these risks were further magnified among like gender twins (ARRs 2.20 and 1.91, respectively).

The risks of very preterm, and neonatal and infant death were increased among all twins for the subfertile group (significant ARRs of 1.36, 1.89, 1.87, respectively) and very preterm, preterm, and birth defects for the IVF group (significant ARRs of 1.28, 1.07, and 1.26, respectively).

Discussion

These analyses of twin pregnancies indicate that compared to fertile women, subfertile and IVF-treated women tend to be older, have more pre-existing chronic conditions, and are at greater risk for adverse pregnancy outcomes, particularly uterine bleeding and placental complications. The twin infants of both subfertile and IVF women are at greater risk for very low birthweight, preterm and very preterm birth; in addition, IVF unlike gender twins are at higher risk for birth defects, and like gender subfertile twins are at higher risk for neonatal and infant death. Some of the difference in risk between subfertile and IVF twin pregnancies may reflect more intensive prenatal monitoring in the latter group (44, 45). Compared to fertile women, the risk of having a primary cesarean delivery was higher in subfertile women and highest in IVF women (as was breech or malpresentation), a finding also reported in prior studies and meta-analyses of IVF pregnancies (16, 46–49). Our findings of an increased risk of preterm birth for IVF twins (ARR 1.07, 95% CI 1.03, 1.12) is nearly identical to the findings from the systematic review by Helmerhorst et al (48) of 1.07, 95% CI 1.02, 1.13. The nonsignificant risk of neonatal death among IVF twins in our study has also been reported by others (48, 50).

A consistent finding in our study and prior studies is the increased risk of bleeding and placental complications in subfertile women and IVF-treated women (51, 52). Compared to fertile women, the risk of placental complications in our study was higher among IVF

women, with significant ARRs ranging from 1.82 to 1.91, and highest among subfertile women, with significant ARRs ranging from 2.00 to 2.20, depending on the gender pair group. Our adverse outcome of placental complications included abruptio placenta, placenta previa or vasa previa, but other placental and cord anomalies not assessed in our study are known to occur more frequently in twin gestations, such as single umbilical artery, velamentous or marginal cord insertion, as well as anomalies unique to twins, such as intraplacental anastomosis and cord entanglement (53, 54). Delbaere et al (54) reported that marginal and velamentous cord insertions, and single umbilical arteries occur more frequently in twins following infertility treatment, increasing in proportion to the invasiveness of the procedure. In their analysis of spontaneous dizygotic twins versus dizygotic twins from assisted conception, the incidence of velamentous cord insertions increased from 3.6% in twins conceived spontaneously to 5% with ovulation induction, 7.4% with IVF, and 10.4% with intracytoplasmic sperm injection (ICSI). Also in their study, the incidence of single umbilical artery increased from 0.6% in spontaneous dizygotic twins to 1.9% with induction of ovulation (AOR 3.19, 95% CI 1.66, 6.11).

In general, most studies show little difference in perinatal outcomes in spontaneously-conceived and subfertile or IVF twins, partially due to failure to control for monozygosity and monochorionicity (16, 49, 55–57). Two-thirds of twins are dizygotic, with 50% being like gender and 50% unlike gender. About one-third of twins are monozygotic (100% being like gender), among these about 70% are also monochorionic (sharing the chorion)—the group at highest risk for morbidity and mortality. In spontaneously-conceived twin pregnancies, the prevalence of dizygotic twinning varies with race and ethnicity, from a low of 1.3/1,000 live births in Asia to 50/1,000 live births in Africa, as well as increasing with the maternal factors of older age, taller height, higher parity, and family history of twinning (58, 59). Prior to the advent of assisted reproductive technologies, the rate of monozygotic twinning was relatively constant worldwide at about 4/1,000 live births, regardless of maternal or familial factors (60); it has been estimated that the incidence has more than doubled with assisted conception (8–9/1,000 live births) (61, 62). In ART treatment, the main risk factor for dizygotic twins and higher-order multiple pregnancies is the transfer of more than one embryo (63, 64), as well as taller maternal stature (>68 inches) and higher number of oocytes retrieved (>8) (65). The risk of monozygotic twinning is increased when culture is extended to the blastocyst stage, and in cleavage stage embryos with assisted hatching (62, 66–73). A recent case-control study from Canada reported that the use of ovarian stimulators alone and with intrauterine insemination greatly increased the risk of multiple births (AORs of 4.5 and 9.32, respectively) (74).

Our findings in unlike gender twins are in accord with several prior studies of dizygotic or unlike gender twins, including higher rates of early preterm birth and neonatal mortality among twins conceived with ovulation induction or IVF (50, 75, 76). In the Dutch study of 6,964 primiparous women who delivered opposite-gender twins (dizygotic) between 2000 and 2012 (76), they also found no difference in rates of pregnancy hypertension, small-for-gestational age birthweight, but an elevated risk of perinatal mortality in the subfertile group (significant in their study, not significant in ours). The results of studies of dizygotic twin pregnancies (75) and unlike gender twin pregnancies (50), also found higher rates of early preterm birth and perinatal mortality in twin pregnancies from ART compared to those from

fertile women, as did our study. Our findings of an increased risk of birth defects and the magnitude of the risk with IVF (ARR 1.26, 95% CI 1.01, 1.59) is in accord with findings from other studies: AOR 1.4, 95% CI 0.9, 2.1 (49); and AOR 1.26, 95% CI 1.14, 1.40 (77).

The relatively small differences in the risks of adverse pregnancy, birth, and infant outcomes of twins by fertility status reported in our study confirm findings reported by others. Higher plurality, though, is associated with much greater risks of pregnancy, birth, and infant adverse health outcomes compared to singletons. Comparing the outcomes in this study to the analysis of 459,623 singleton births in the MOSART project during this same time period (2004–10) (38), show the manifold increased risks of twins compared to singletons. Born an average of 3 V weeks earlier and 950 grams lighter, twins were more than ten times as likely to be born very low birthweight, low birthweight, or early preterm, and eight times more likely to be born preterm. The mothers of twins were about twice as likely to develop gestational diabetes, pregnancy hypertension, or uterine bleeding, and were more than four times as likely to be hospitalized prenatally. Placental complications were more than twice as likely with twins and primary cesarean delivery three times more likely. The risk of neonatal death was more than seven times greater and the risk of infant death more than five times greater for twins compared to singletons.

The risk of severe maternal morbidity has also been evaluated in the MOSART study (34). Among IVF-treated women, the risk of severe maternal morbidity was more than threefold higher with twins than with singletons; among all births, the risk of severe maternal morbidity was more than fourfold higher for twins versus singletons (46.5/1,000 twin deliveries versus 10.5/1,000 singleton deliveries). In a nationwide study in the Netherlands, Witteveen et al (78) also reported a fourfold increased risk of severe maternal morbidity in multiple versus singleton births, as well a twofold increase with assisted reproductive technology. Iatrogenic multiple births are acknowledged as the most important adverse outcome of IVF treatment (40, 79, 80). By periodically issuing national guidelines on the number of embryos to transfer, the Society for Assisted Reproductive Technology has been able to dramatically reduce the rate of higher-order multiples, although the rate of twins remains high (1).

There are a number of preventive measures that should be incorporated into prenatal care to improve the course and outcome of twin gestations. Accurate gestational dating and determination of chorionicity should be done prior to 14 weeks gestation, with more intensified monitoring and earlier planned delivery for monochorionic pregnancies (81–83). Supplementation with folate and multivitamins has been shown to improve outcomes in IVF pregnancies, and reduce the risk for birth defects, as well as velamentous and marginal cord insertions, and prematurity (84–89). Achieving BMI-specific weight gains by specific gestational periods (by 20 weeks, by 28 weeks, and at 36–38 weeks), is associated with better fetal growth, longer gestations, and fewer pregnancy-related complications in twins (90–93).

Strengths and Limitations

In this study we are comparing outcomes for non-IVF fertility treatment with IVF fertility treatment vs conceptions with no fertility treatment. We don’t really know if it is a

comparison of women with subfertile vs fertile women. The fertile group could include women who had subfertility and conceived without treatment. The direction of bias may likely be to lessen the magnitude of any differences seen, if the subfertility is in itself a risk factor for complications which is likely true from other data. 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 (6, 8, 40, 94, 95). Prior studies (56, 94, 95) have relied on linkages between IVF cycles and vital records using only maternal and infant dates of birth, or probabilistic algorithms (40, 95). Although there is a high degree of comparability between the SART CORS and vital records (36), 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 (6, 8, 40), and we have additionally validated the SART CORS variables with the MOSART study (36). 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. 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. Another limitation of this study is our inability to identify chorionicity and zygosity in our study population. By grouping twins by gender pair combinations, all monozygotic twins were included in the like gender group, and dizygotic twins were included in the unlike gender group. Approximately half of all like gender twins are monozygotic and half are dizygotic.

Conclusions

Risks of all maternal and most infant adverse outcomes are increased for subfertile and IVF twins. Among all twins, the highest risks were for uterine bleeding and placental complications for the subfertile and IVF groups, and neonatal and infant death in the subfertile group. These findings provide further evidence supporting single embryo transfer and more cautious use of ovulation induction.

Acknowledgments

SART wishes to thank all of its members for providing clinical information to the SART CORS database for use by patients and researchers. Without the efforts of our members, this research would not have been possible.

The project described was supported by grant R01HD067270 from the National Institute of Child Health and Human Development. The content is solely the responsibility of the authors and does not necessarily represent the

official views of the National Institute of Child Health and Human Development or the National Institutes of Health.

References

1. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Mathews TJ. Births: Final data for 2015. National Vital Statistics Reports. Jan 5.2017 66(1)
2. Schieve LA, Peterson HB, Meikle SF, Jeng G, Danel I, Burnett NM, Wilcox LS. Live-birth rates and multiple birth risk using in vitro fertilization. JAMA. 1999; 282:1832–8. [PubMed: 10573274]
3. Nakhuda GS, Sauer MV. Addressing the growing problem of multiple gestations created by assisted reproductive therapies. Seminars in Perinatology. 2005; 29:355–362. [PubMed: 16360495]
4. Sutcliffe AG, Ludwig M. Outcome of assisted reproduction. The Lancet. 2007; 370:351–59.
5. Kulkarni AD, Jamieson DJ, Jones HW, Kissin DM, Gallo MF, Macaluso M, Adashi EY. Fertility treatments and multiple births in the United States. New England Journal of Medicine. 2013; 369:2218–25. [PubMed: 24304051]
6. Sunderam S, Kissin DM, Crawford SB, Folger SG, Jamieson DJ, Warner L, Barfield WD. Assisted reproductive technology surveillance—United States, 2013. Morbidity and Mortality Weekly Report Surveillance Summary. 2015; 64(11):1–26.
7. Kupka MS, D'Hooghe T, Ferraretti AP, deMouzon J, Erb K, Castilla JA, Calhaz-Jorge C, De Geyter C, Goossens V. Assisted reproductive technology in Europe, 2011: Results generated from European registers by ESHRE. Human Reproduction. 2016; 31:233–248. [PubMed: 26740578]
8. Center for Disease Control and Prevention, American Society for Reproductive Medicine, and Society for Assisted Reproductive Technology. 2011 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. Washington, DC: US Dept. of Health and Human Services; 2013.
9. D'Angelo DV, Whitehead N, Helms K, Barfield W, Ahluwalia IB. Birth outcomes of intended pregnancies among women who used assisted reproductive technology, ovulation stimulation, or no treatment. Fertility and Sterility. 2011; 96:314–20. [PubMed: 21718990]
10. Merritt TA, Goldstein M, Philips R, Peverini R, Iwakoshi J, Rodriguez A, Oshiro B. Impact of ART on pregnancies in California: An analysis of maternity outcomes and insights into the added burden of neonatal intensive care. Journal of Perinatology. 2014; 34:345–50. [PubMed: 24556981]
11. Opdahl S, Henningsen AA, Tiitinen A, Bergh C, Pinborg A, Romundstad PR, Wennerholm UB, Gissler M, Skjærven R, Romundstad LB. Risk of hypertensive disorders in pregnancies following assisted reproductive technology: A cohort study from the CoNARTaS group. Human Reproduction. 2015; 30:1724–31. [PubMed: 25924655]
12. Qin J, Wang H, Sheng X, Liang D, Tan H, Xia J. Pregnancy-related complications and adverse pregnancy outcomes in multiple pregnancies resulting from assisted reproductive technologies: A meta-analysis of cohort studies. Fertility and Sterility. 2015; 103:1492–508. [PubMed: 25910567]
13. Luke S, Sappenfield WM, Kirby RS, McKane P, Bernson D, Zhang Y, Chuong F, Cohen B, Boulet SL, Kissin DM. The impact of ART on live birth outcomes: Differing experiences across three States. Paediatric and Perinatal Epidemiology. 2016; 30:209–16. [PubMed: 26913961]
14. Hayashi M, Nakai A, Satoh S, Matsuda Y. Adverse obstetric and perinatal outcomes of singleton pregnancies may be related to maternal factors associated with infertility rather than the type of assisted reproductive technology procedure used. Fertility and Sterility. 2012; 98:922–8. [PubMed: 22763098]
15. Luke B, Stern JE, Hornstein MD, Kotelchuck M, Diop H, Cabral H, Declercq ER. Is the wrong question being asked in infertility research? Journal of Assisted Reproduction and Genetics. 2016; 33(1):3–8. [PubMed: 26634257]
16. DoPierala AL, Bhatta S, Raja EA, Bhattacharya S, Bhattacharya S. Obstetric consequences of subfertility: A retrospective study. BJOG. 2016; 123:1320–8. [PubMed: 26335260]
17. Kondapalli LA, Perales-Puchalt A. Low birth weight: Is it related to assisted reproductive technology or underlying infertility? Fertility and Sterility. 2013; 99:303–10. [PubMed: 23375144]

18. Song S, Ghosh J, Mainigi M, Turan N, Weinerman R, Truongcao M, Coutifaris C, Sapienza C. DNA methlation differences between in vitro- and in vivo-conceived children are associated with ART procedures rather than infertility. Clinical Epigenetics. 2015; 7:41. [PubMed: 25901188]
19. Shih W, Rushford DD, Bourne H, Garrett C, McBain JC, Healy DL, Baker HWG. Factors affecting low birthweight after assisted reproduction technology: difference between transfer of fresh and cryopreserved embryos suggests an adverse effect of oocyte collection. Human Reproduction. 2008; 23:1644–53. [PubMed: 18442997]
20. Wennerholm UB, Henningsen AK, Romundstad LB, Bergh C, Pinborg A, Skjaerven R, et al. Perinatal outcomes of children born after frozen-thawed embryo transfer: A Nordic cohort study from the CoNARTaS group. Human Reproduction. 2013; 28:2545–53. [PubMed: 23832793]
21. Marino JL, Moore VM, Willson KJ, Rumbold A, Whitrow MJ, Giles LC, Davies MJ. Perinatal outcomes by mode of assisted conception and sub-fertility in an Australian data linkage cohort. PLOS ONE. 2014; 9:e80398.doi: 10.1371/journal.pone.0080398 [PubMed: 24416127]
22. Kotelchuck M, Hoang L, Stern JE, Diop D, Belanoff C, Declercq E. The MOSART database: Linking the SART CORS clinical database to the population-based Massachusetts PELL reproductive public health data system. Maternal and Child Health Journal. 2014; doi: 10.1007/s10995-014-1465-4
23. Stern JE, Brown MB, Wantman E, Kalra S, Luke B. Live birth rates and birth outcomes by diagnosis using linked cycles from the SART CORS database. Journal of Assisted Reproduction and Genetics. 2013; 30:1445–50. [PubMed: 24014215]
24. Declercq ER, Belanoff C, Diop H, Gopal D, Hornstein MD, Kotelchuck M, Luke B, Stern JE. Identifying women with indicators of subfertility in a statewide population database: Operationalizing the missing link in ART research. Fertility and Sterility. 2014; 101:463–71. [PubMed: 24289994]
25. Stern JE, Kotelchuck M, Luke B, Declercq E, Cabral H, Diop H. Calculating length of gestation from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database versus vital records may alter reported rates of prematurity. Fertility and Sterility. 2014; 101:1315–20. [PubMed: 24786746]
26. Getz KD, Liberman RF, Luke B, Stern JE, Declercq E, Anderka MT. The occurrence of birth defects in relation to assisted reproductive technologies in the Massachusetts Outcomes Study of Assisted Reproductive Technology database. Fertility and Sterility. 2014; 102:e4. [PubMed: 24907911]
27. Stern JE, Luke B, Hornstein MD, Cabral H, Gopal D, Diop H, Kotelchuck M. The effect of father's age in fertile, subfertile, and assisted reproductive technology pregnancies: A population based cohort study. Journal of Assisted Reproduction and Genetics. 2014; 31:1437–44. [PubMed: 25193289]
28. Declercq E, Luke B, Belanoff C, Cabral H, Diop H, Gopal D, Hoang L, Kotelchuck M, Stern JE, Hornstein MD. Perinatal Outcomes Associated with Assisted Reproductive Technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). Fertility and Sterility. 2015; 103:888–895. [PubMed: 25660721]
29. Stern JE, Luke B, Tobias M, Gopal D, Hornstein MD, Diop H. Adverse pregnancy and birth outcomes by infertility diagnoses with and without ART treatment. Fertility and Sterility. 2015; 103:1438–45. [PubMed: 25813277]
30. Luke B, Stern JE, Kotelchuck M, Declercq ER, Hornstein MD, Gopal D, Hoang L, Diop H. Adverse pregnancy outcomes after in vitro fertilization: Effect of number of embryos transferred and plurality at conception. Fertility and Sterility. 2015; 104:79–86. [PubMed: 25956368]
31. Declercq ER, Luke B, Stern JE, Diop H, Gopal D, Cabral H, Belanoff C, Kotelchuck M. Maternal Postpartum Hospitalization Following ART Births (Research letter). Epidemiology. 2015; 26:e64–65. [PubMed: 26317669]
32. Luke B, Stern JE, Kotelchuck M, Declercq E, Cohen B, Diop H. Birth outcomes by infertility diagnosis: Analyses of the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). Journal of Reproductive Medicine. 2015; 60:480–490. [PubMed: 26775455]
33. Diop H, Gopal D, Cabral H, Belanoff C, Declercq ER, Kotelchuck M, Luke B, Stern JE. Assisted reproductive technology and Early Intervention enrollment. Pediatrics. 2016; 137(3):e20152007. [PubMed: 26908668]

34. Belanoff C, Declercq ER, Diop H, Gopal D, Kotelchuck M, Luke B, Nguyen T, Stern JE. Severe maternal morbidity and the use of assisted reproductive technology. Obstetrics and Gynecology. 2016; 127:527–534. [PubMed: 26855105]
35. Luke B, Stern JE, Kotelchuck M, Declercq E, Anderka M, Diop H. Birth outcomes by infertility treatment: Analyses of the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). Journal of Reproductive Medicine. 2016; 61:114–127. [PubMed: 27172633]
36. Stern JE, Gopal D, Anderka M, Liberman R, Kotelchuck M, Luke B. Validation of birth outcomes in the SART CORS: Population-based analysis from the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART). Fertility and Sterility. 2016; 106:717–722.e2. [PubMed: 27208695]
37. Luke B, Gopal D, Cabral H, Diop H, Stern JE. Perinatal outcomes of singleton siblings: The effects of maternal fertility status and ART treatment. Journal of Assisted Reproduction and Genetics. 2016; 33:1203–13. [PubMed: 27318927]
38. Luke B, Gopal D, Cabral H, Stern JE, Diop H. Pregnancy, birth, and infant outcomes by maternal fertility status: The Massachusetts Outcomes Study of Assisted Reproductive Technology. American Journal of Obstetrics and Gynecology. in press.
39. Toner JP, Coddington CC, Doody K, Van Voorhis B, Seifer DB, Luke B, Wantman E. Society for Assisted Reproductive Technology and assisted reproductive technology in the United States: A 2016 update. Fertility and Sterility. 2016; 106:541–6. [PubMed: 27301796]
40. Center for Disease Control and Prevention, American Society for Reproductive Medicine, and Society for Assisted Reproductive Technology. 2012 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. Washington, DC: US Dept. of Health and Human Services; 2014.
41. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatrics. 2003; 3:6–16. [PubMed: 12848901]
42. Land JA. How should we report on perinatal outcome? Human Reproduction. 2006; 21:2638–9. BMJ 2002; 325:157-160. [PubMed: 16829595]
43. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004; 159:702–706. [PubMed: 15033648]
44. Srebnik N, Miron-Shatz T, Rolison JJ, Hanoch Y, Tsafrir A. Physician recommendation for invasive prenatal testing: the case of the ‘precious baby’. Human Reproduction. 2013; 28:3007–11. [PubMed: 24045783]
45. Minkoff HL, Berkowitz R. The myth of the precious baby. Obstetrics and Gynecology. 2005; 106:607–9. [PubMed: 16135595]
46. Reubinoff BE, Samueloff A, Ben-Haim M, Friedler S, Schenker JG, Lewin A. Is the obstetric outcome of in vitro fertilized singleton gestations different from natural ones? A controlled study. Fertility and Sterility. 1997; 67:1077–83. [PubMed: 9176447]
47. Sullivan EA, Chapman MG, Wang YA, Adamson GD. Population-based study of cesarean section after in vitro fertilization in Australia. Birth. 2010; 37:184–91. [PubMed: 20887534]
48. Helmerhorst FM, Perquin DAM, Donker D, Keirse MJNC. Perinatal outcome of singletons and twins after assisted conception: A systematic review of controlled studies. BMJ. 2004; 328:261. [PubMed: 14742347]
49. McDonald S, Murphy K, Beyene J, Ohlsson A. Perinatal outcomes of in vitro fertilization twins: A systematic review and meta-analyses. American Journal of Obstetrics and Gynecology. 2005; 193:141–52. [PubMed: 16021072]
50. Hansen M, Colvin L, Petterson B, Kurinczuk JJ, de Klerk N, Bower C. Twins born following assisted reproductive technology: Perinatal outcome and admission to hospital. Human Reproduction. 2009; 24:2321–31. [PubMed: 19458317]
51. Schieve LA, Cohen B, Nannini A, Ferre C, Reynolds MA, Zhang Z, Jeng G, Macaluso M, Wright VC. A population-based study of maternal and perinatal outcomes associated with assisted reproductive technology in Massachusetts. Maternal and Child Health Journal. 2007; 11:517–25. [PubMed: 17345154]

52. Castera D, Bordi G, Stegagno M, Filippini F, Podagrosi M, Roselli D, Moscarini M. Maternal and perinatal outcomes in spontaneous versus assisted conception twin pregnancies. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014; 174:64–69. [PubMed: 24405729]
53. Hubinont C, Lewi L, Bernard P, Marbaix E, Debiève F, Jauniaux E. Anomalies of the placenta and umbilical cord in twin gestations. American Journal of Obstetrics and Gynecology. 2015; 213:S91–S102. [PubMed: 26428508]
54. Delbaere I, Goetgeluk S, Derom C, De Bacquer D, De Sutter P, Temmerman M. Umbilical cord anomalies are more frequent in twins after assisted conception. Human Reproduction. 2007; 22:2763–7. [PubMed: 17720701]
55. Murphy MFG, Neale RE, Hey K, Seagroatt VA, Goldacre MJ, Vessey MP, Willis BM, Ellis JD, Barlow DH. Pregnancy outcome among twins conceived after subfertility treatment compared with natural twins: A population-based study. Twin Research and Human Genetics. 2006; 9:279–84. [PubMed: 16611499]
56. Boulet SL, Schieve LA, Nannini A, Ferre C, Devine O, Cohen B, Zhang Z, Wright V, Macaluso M. Perinatal outcomes of twin births conceived using assisted reproduction technology: A population-based study. Human Reproduction. 2008; 23:1941–8. [PubMed: 18487216]
57. Anbazhagan A, Hunter A, Breathnach FM, Mcauliffe FM, Geary MP, Daly S, Higgins JR, Morrison JJ, Burke G, Higgins S, Dicker P, Tully E, Carroll S, Malone FD. Comparison of outcomes of twins conceived spontaneously and by artificial reproductive therapy. Journal of Maternal-Fetal & Neonatal Medicine. 2014; 27:458–62. [PubMed: 23865515]
58. White C, Wyshak G. Inheritance in human dizygotic twinning. New England Journal of Medicine. 1964; 271:1003–5. [PubMed: 14198054]
59. MacGillivray I. Epidemiology of twin pregnancy. Seminars in Perinatology. 1986; 10:4–8. [PubMed: 3764449]
60. Bulmer, MC. The biology of twinning. London: Oxford University Press; 1970.
61. Chan OTM, Mannino FL, Benirschke K. A retrospective analysis of placentas from twin pregnancies derived from assisted reproductive technology. Twin Research and Human Genetics. 2007; 10:385–393. [PubMed: 17564529]
62. Vitthala S, Gelbaya TA, Brisonn DR, Fitzgerald CT, Nardo LG. The risk of monozygotic twins after assisted reproductive technology: A systematic review and meta-analysis. Human Reproduction. 2009; 15:45–55.
63. Practice Committee of the American Society for Reproductive Medicine. Multiple gestation associated with infertility therapy: An American Society for Reproductive Medicine Practice Committee opinion. Fertility and Sterility. 2012; 97:825–34. [PubMed: 22192352]
64. Luke B, Stern JE, Kotelchuck M, Declercq ER, Hornstein MD, Gopal D, Hoang L, Diop H. Adverse pregnancy outcomes after in vitro fertilization: Effect of number of embryos transferred and plurality at conception. Fertility and Sterility. 2015; 104:79–86. [PubMed: 25956368]
65. Groeneveld E, Lambers MJ, Stakelbeek MEF, Mooij TM, van den Belt-Dusebout AW, Heymans MW, Schats R, Hompes PGA, Hoek A, Burger CW, van Leeuwen FE, Lambalk CB. Factors associated with dizygotic twinning after IVF treatment with double embryo transfer. Human Reproduction. 2012; 27:2966–70. [PubMed: 22786776]
66. Chow JS, Benson CB, Racowsky C, Doubilet PM, Ginsburg E. Frequency of a monochorionic pair in multiple gestations: Relationship to mode of conception. Journal of Ultrasound in Medicine. 2001; 20:757–60. [PubMed: 11444734]
67. Toledo MG. Is there increased risk of monozygotic twinning after assisted reproductive technology? Australia and New Zealand Journal of Obstetrics and Gynaecology. 2005; 45:360–4.
68. Skiadas CC, Missmer SA, Benson CB, Gee RE, Racowsky C. Risk factors associated with pregnancies containing a monochorionic pair following assisted reproductive technologies. Human Reproduction. 2008; 23:1366–71. [PubMed: 18378561]
69. Luke B, Brown MB, Wantman E, Stern JE. Factors associated with monozygosity in assisted reproductive technology (ART) pregnancies and the risk of recurrence using linked cycles Fertility and Sterility. 2014; 101:683–9.

70. Knopman JM, Krey LC, Oh C, Lee J, McCaffrey C, Noyes N. What makes them split? Identifying risk factors that lead to monozygotic twins after in vitro fertilization. Fertility and Sterility. 2014; 102:82–9. [PubMed: 24794318]
71. Vaughn DA, Ruthazer R, Penzias AS, Norwitz ER. Clustering of monozygotic twinning in IVF. Journal of Assisted Reproduction and Genetics. 2016; 33:19–26. [PubMed: 26582330]
72. Nakasuji T, Saito H, Araki R, Nakaza A, Nakashima A, Kuwahara A, Ishihara O, Irahara M, Kubota T, Yoshimura Y, Sakumoto T. The incidence of monozygotic twinning in assisted reproductive technology: analysis based on results from the 2010 Japanese ART national registry. Journal of Assisted Reproduction and Genetics. 2014; 31:803–7. [PubMed: 24722789]
73. Sotiroska V, Petanovski Z, Dimitrov G, Hadji-Lega M, Shushlesi D, Saltirovski S, Matevski V, Shenbakar S, Panov S, Johansson L. The day of embryo transfer affects delivery rate, birth weights, female-to-male ratio, and monozygotic rate. Taiwanese Journal of Obstetrics & Gynecology. 2015; 54:716–21. [PubMed: 26700991]
74. Chaabane S, Sheehy O, Monnier P, Bissonnette F, Trasler JM, Fraser W, Béard A. Association between ovarian stimulators with and without intrauterine insemination, and assisted reproductive technologies on multiple births. American Journal of Obstetrics and Gynecology. 2015; 213:511.e1–14. [PubMed: 26079626]
75. Lambalk CB, van Hooff M. Natural versus induced twinning and pregnancy outcome: A Dutch nationwide survey of primiparous dizygotic twin deliveries. Fertility and Sterility. 2001; 75:731–6. [PubMed: 11287027]
76. Bensdorp AJ, Hukkelhoven CW, van der Veen F, Mol BWJ, Lambalk CB, van Wely M. Dizygotic twin pregnancies after medically assisted reproduction and after natural conception: Maternal and perinatal outcomes. Fertility and Sterility. 2016; 106:371–7. [PubMed: 27108393]
77. Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, Chan A. Reproductive technologies and the risk of birth defects. New England Journal of Medicine. 2012; 366:1803–13. [PubMed: 22559061]
78. Witteveen T, Van Den Akker T, Zwart JJ, Bloemenkamp KW, Roosmalen JV. Severe acute maternal morbidity in multiple pregnancies: A nationwide cohort study. American Journal of Obstetrics and Gynecology. 2016; 214:641.e1–10. [PubMed: 26576487]
79. Sutcliffe AG, Ludwig M. Outcome of assisted reproduction. Lancet. 2007; 370:351–9. [PubMed: 17662884]
80. Nakhuda GS, Sauer MV. Addressing the growing problem of multiple gestations created by assisted reproductive therapies. Semin Perinatol. 2005; 29:355–62. [PubMed: 16360495]
81. Multifetal gestations: Twin, triplets, and higher-order multifetal pregnancies. American College of Obstetricians and Gynecologists Obsteterics and Gynecology. 2016; 128:e131–46.Practice Bulletin No. 169
82. Dias T, Arcangeli T, Bhide A, Napolitano R, Mahsud-Dornan S, Thilaganathan B. First-trimester ultrasound determination of chorionicity in twin pregnancy. Ultrasound in Obstetrics and Gynecology. 2011; 38:530–2. [PubMed: 21308842]
83. Maruotti GM, Saccone G, Morlando M, Martinelli P. First-trimester ultrasound determination of chorionicity in twin gestations using the lambda sign: A systematic review and meta-analysis. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2016; 202:66–70. [PubMed: 27180271]
84. Haggarty P, McCallum H, McBain H, Andrews K, Duthie S, McNeill G, Templeton A, Haites N, Campbell D, Bhattacharya S. Effect of B vitamins and genetics on success of in-vitro fertilization: Prospective cohort study. Lancet. 2006; 367:1513–1519. [PubMed: 16679164]
85. US Preventive Services Task Force. Folic acid supplementation for the prevention of neural tube defects. JAMA. 2017; 317:183–9. [PubMed: 28097362]
86. Catov JM, Nohr EA, Bodnar LM, Knudson VK, Olsen SF, Olsen J. Association of periconceptional multivitamin use with reduced risk of preeclampsia among normal-weight women in the Danish National Birth Cohort. American Journal of Epidemiology. 2009; 169:1304–1311. [PubMed: 19372217]

87. Scholl TO, Hediger ML, Bendich A, Schall JI, Smith WK, Krueger PM. Use of multivitamin/mineral prenatal supplements: Influence on the outcome of pregnancy. American Journal of Epidemiology. 1997; 146:134–141. [PubMed: 9230775]

88. Nilsen RM, Vollset SE, Rasmussen SA, Ueland PM, Daltveit AK. Folic acid and multivitamin supplement use and risk of placental abruption: a population-based registry study. Am J Epidemiol. 2008; 167:867–874. [PubMed: 18187445]

89. Ebbing C, Kiserud T, Johnsen SL, Albrechtsen S, Rasmussen S. Prevalence, risk factors and outcomes of velamentous and cord insertions: A population-based study of 634,741 pregnancies. PLOS One. 2013; 8:e70380. [PubMed: 23936197]

90. Luke B, Hediger ML, Nugent C, Newman RB, Mauldin JG, Witter FR, O'Sullivan MJ. Body mass index-specific weight gains associated with optimal birth weights in twin pregnancies. Journal of Reproductive Medicine. 2003; 48:217–224. [PubMed: 12746982]

91. Fox NS, Stern EM, Saltzman DH, Klauser CK, Gupta S, Rebarber A. The association between maternal weight gain and spontaneous preterm birth in twin pregnancies. Journal of Maternal-Fetal & Neonatal Medicine. 2014; 27:1652–5. [PubMed: 24593699]

92. Pettit KE, Lacoursiere DY, Schrimmer DB, Alblewi H, Moore TR, Ramos GA. The association of inadequate mid-pregnancy weight gain and preterm birth in twin pregnancies. Journal of Perinatology. 2015; 35:85–9. [PubMed: 25166622]

93. Luke B. Nutrition for multiples. Clinical Obstetrics and Gynecology. 2015; 58:585–610. [PubMed: 26125961]

94. Zhang Z, Macaluso M, Cohen B, Schieve L, Nannini A, Chen M, Wright V. Accuracy of assisted reproductive technology information on the Massachusetts birth certificate, 1997–2000. Fertility and Sterility. 2010; 94:1657–61. [PubMed: 20004392]

95. Mneimneh AS, Boulet SL, Sunderam S, Zhang YJ, Jamieson DJ, Crawford S, McKane P, Copeland G, Mersol-Barg M, Grigorescu V, Cohen B, Steele J, Sappenfield W, Diop H, Kirby RS, Kissin DM. States Monitoring Assisted Reproductive Technology (SMART) Collaborative: Data collection, linkage, dissemination, and use. Journal of Women's Health. 2013; 22:571–7.

Condensation

Risks among subfertile and IVF twins were increased, highest for uterine bleeding and placental complications; and neonatal and infant death among like gender twinsborn to subfertile women.

Table 1

Maternal and Paternal Demographic Characteristics by Maternal Fertility Group and Infant Gender Combinations

		All Twins				Like Gender Pairs			Unlike Gender Pairs		
		All Groups	**Fertile**	**Subfertile**	**IVF**	**Fertile**	**Subfertile**	**IVF**	**Fertile**	**Subfertile**	**IVF**
	N, pregnancies	**10,352**	**6,090**	**724**	**3,538**	**4,150**	**391**	**1,817**	**1,940**	**333**	**1,721**
Maternal	Mean (SD)	32.3 (5.8)	30.4 (5.7)	34.2 (4.5)	35.3 (4.6)	30.1 (5.7)	34.6 (4.4)	35.4 (4.6)	30.9 (5.5)	33.7 (4.6)	35.3 (4.6)
Age (years)	(%) <35	63.1	75.1	54.4	44.4	76.5	51.4	43.6	72.1	58.0	45.1
	35–37	19.5	15.7	23.2	25.4	14.6	23.3	24.8	18.1	23.1	26.0
	38–40	11.2	7.1	15.3	17.5	6.8	16.9	18.6	7.7	13.5	16.3
	41–42	3.2	1.4	3.9	6.3	1.4	4.4	6.8	1.4	3.3	5.8
	≥43	2.9	0.7	3.2	6.5	0.7	4.1	6.2	0.8	2.1	6.8
Paternal	Mean, SD	34.9 (6.5)	33.1 (6.5)	36.6 (5.7)	37.4 (5.8)	32.9 (6.5)	36.9 (5.9)	37.5 (5.9)	33.6 (6.4)	36.2 (5.6)	37.3 (5.7)
Age (years)	(%) <35	48.6	59.5	39.4	33.1	60.9	38.0	32.4	56.6	41.0	33.8
	35–37	20.7	18.6	23.1	23.6	18.4	20.8	22.1	19.0	25.7	25.2
	38–40	13.5	10.5	16.7	17.6	9.9	18.5	18.6	11.6	14.7	16.6
	41–42	6.4	4.7	7.9	8.7	4.4	7.8	9.4	5.3	8.0	8.0
	≥43	10.8	6.7	12.9	16.9	6.4	14.8	17.5	7.5	10.7	16.3
Maternal Race	Hispanic	8.7	12.3	3.0	3.6	12.6	3.3	3.4	11.6	2.7	3.9
& Ethnicity (%)	White	76.6	69.8	87.7	85.9	69.2	88.0	86.2	71.2	87.4	85.5
	Black	7.4	10.7	2.2	2.9	10.5	1.5	2.9	11.3	3.0	2.8
	Asian	5.5	4.8	5.7	6.5	5.4	5.4	6.4	3.6	6.0	6.7
	Other	1.9	2.4	1.4	1.1	2.4	1.8	1.1	2.4	0.9	1.1
Paternal Race	Hispanic	8.0	11.7	3.5	3.2	12.5	3.9	2.9	9.8	3.1	3.4
& Ethnicity (%)	White	77.9	71.1	87.2	86.8	69.7	87.8	87.2	74.2	86.5	86.3
	Black	7.4	10.6	2.5	3.2	10.6	1.8	3.1	10.5	3.4	3.3
	Asian	5.1	4.6	5.5	5.8	5.1	5.2	5.8	3.5	5.8	5.8
	Other	1.7	2.1	1.3	1.0	2.2	1.3	.9	1.9	1.2	1.1
Maternal	<HS or HS/GED	23.5	33.4	11.5	8.8	33.6	10.5	9.3	33.1	12.7	8.3
Education (%)	Some College	19.6	22.0	16.0	16.1	22.7	15.6	15.0	20.5	16.6	17.3
	BS or Graduate	56.9	44.6	72.5	75.1	43.7	73.9	75.7	46.4	70.8	74.4

		All Twins				Like Gender Pairs			Unlike Gender Pairs		
		All Groups	**Fertile**	**Subfertile**	**IVF**	**Fertile**	**Subfertile**	**IVF**	**Fertile**	**Subfertile**	**IVF**
	N, pregnancies	**10,352**	**6,090**	**724**	**3,538**	**4,150**	**391**	**1,817**	**1,940**	**333**	**1,721**
Paternal	<HS or HS/GED	28.8	38.5	18.7	15.1	39.4	19.2	15.2	36.6	18.1	15.1
Education (%)	Some College	15.6	17.7	12.5	12.9	17.8	11.7	12.4	17.7	13.5	13.3
	BS or Graduate	55.6	43.7	68.8	72.0	42.8	69.1	72.4	45.7	68.4	71.6
Maternal	Yes	4.4	7.0	1.0	0.7	6.2	1.3	0.7	8.6	0.6	0.6
Smoking (%)	No	95.6	93.0	99.0	99.4	93.8	98.7	99.3	91.4	99.4	99.4
Payor	Private	74.0	59.6	93.7	94.7	60.0	93.4	94.2	58.8	94.0	95.2
Source (%)	Public	24.3	38.6	5.4	3.4	38.4	5.9	3.6	39.0	4.8	3.1
	Self-pay or Free	1.8	1.8	1.0	1.9	1.6	0.8	2.2	2.2	1.2	1.6

All comparisons across fertility groups were significant at $p<0.0001$

Table 2

IVF Factors (%) by Infant Gender Combination Groups

	All Twins	Like Gender Pairs	Unlike Gender Pairs	P Values
N (pairs)	3,538	1,817	1,721	Like vs Unlike Gender Pairs
Prior IVF cycles	54.3	54.6	54.0	0.71
Mean number of IVF cycles (SD)	1.34 (1.81)	1.40 (1.93)	1.28 (1.67)	0.06
Oocyte Source-donor	12.0	11.8	12.1	0.81
autologous	88.0	88.2	87.9	
Embryo State-frozen	10.0	10.5	9.4	0.28
fresh	90.0	89.5	90.6	
Embryos transferred =1	1.1	1.9	0.2	<.0001
Embryos transferred =2	70.4	69.7	71.2	
Embryos transferred >2	28.5	28.4	28.6	
Number of fetal heartbeats =1	0.4	0.6	0.3	
Number of fetal heartbeats =2	94.1	94.1	94.2	
Number of fetal heartbeats >2	5.4	5.4	5.5	0.49
Infertility Diagnosis				
Male Factor	32.1	32.2	32.1	0.94
Endometriosis	7.3	6.9	7.7	0.33
Ovulation Disorders	14.2	13.9	14.5	0.58
Diminished Ovarian Reserve	11.1	10.9	11.2	0.76
Tubal Factors	12.4	12.4	12.3	0.87
Uterine Factors	2.6	2.9	2.3	0.32
Other Factors	14.7	14.5	14.9	0.73
Unexplained	23.7	23.7	23.6	0.99

Table 3

Pregnancy, Birth, and Infant Outcomes by Maternal Fertility Group and Infant Gender Combinations

		All Twins				Like Gender Pairs			Unlike Gender Pairs			P Values		
		All Groups	Fertile	Subfertile	IVF	Fertile	Subfertile	IVF	Fertile	Subfertile	IVF	Across Groups		
	N, pregnancies	**10,352**	**6,090**	**724**	**3,538**	**4,150**	**391**	**1,817**	**1,940**	**333**	**1,721**			
	N, infants	**20,703**	**12,179**	**1,448**	**7,076**	**8,300**	**782**	**3,634**	**3,879**	**666**	**3,442**	**All**	**Like**	**Unlike**
	Groups	**All**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**1–2–3**	**4–5–6**	**7–8–9**
Pre-existing	Diabetes (%)	1.9	1.7	2.4	2.2	1.8	2.3	2.6	1.5	2.4	1.7	NS	NS	NS
Conditions	Chronic hypertension (%)	2.8	2.6	2.9	3.2	2.5	2.8	2.9	2.6	3.0	3.4	NS	NS	NS
Parity	Nulliparous (%)	25.5	**20.9**	**28.8**	**32.2**	**20.9**	**29.2**	**32.6**	**20.7**	**28.0**	**32.0**	***	***	***
Pregnancy	Gestational diabetes (%)	9.2	**8.1**	**11.6**	**10.7**	**8.3**	**10.0**	**10.3**	**7.6**	**13.5**	**11.0**	***	*	***
Conditions	Pregnancy hypertension (%)	22.7	**20.5**	**26.7**	**25.5**	**20.1**	**28.4**	**25.3**	**21.4**	**24.6**	**25.6**	***	***	**
	Prenatal hospitalization (%)	16.2	15.8	17.4	16.5	16.3	16.1	17.1	14.8	18.9	16.0	NS	NS	NS
	Uterine bleeding (%)	1.7	**1.0**	**1.9**	**2.9**	**1.0**	**2.3**	**2.6**	**1.1**	**1.5**	**3.2**	***	***	***
Labor and	Breech/Malpresentation (%)	31.6	**30.5**	**28.4**	**34.0**	**29.2**	**26.4**	**32.3**	33.3	30.6	35.7	**	*	NS
Delivery	Cephalopelvic Disproportion (%)	0.9	0.8	1.2	1.0	0.9	1.3	1.2	0.7	1.2	0.9	NS	NS	NS
Factors	Abruptio placenta (%)	2.5	2.2	3.7	2.8	2.2	3.8	2.8	2.3	3.6	2.8	*	NS	NS
	Placenta previa (%)	1.3	**0.7**	**2.1**	**2.2**	**0.9**	**2.1**	**2.4**	**0.4**	**2.1**	**2.0**	***	***	***
	Vasa previa (%)	0.17	0.13	0.28	0.23	0.17	0.51	0.22	0.05	0.0	0.23	NS	NS	NS
	Other excessive bleeding (%)	1.5	**1.2**	**2.2**	**1.8**	**1.2**	**2.8**	**2.0**	1.0	1.5	1.7	**	**	NS
	Placental complications[1] (%)	3.9	**3.0**	**5.9**	**5.1**	**3.0**	**6.1**	**5.3**	**2.7**	**5.7**	**4.9**	***	***	**
Mode of	Vaginal[2] (%)	27.8	**31.3**	**28.3**	**21.5**	**31.6**	**30.4**	**23.3**	**30.6**	**25.8**	**19.7**			
Delivery	Primary cesarean (%)	57.6	**52.8**	**60.2**	**65.4**	**52.6**	**58.8**	**64.2**	**53.1**	**61.9**	**66.7**	***	***	***
	Repeat cesarean (%)	14.6	**15.9**	**11.5**	**13.1**	**15.7**	**10.7**	**12.6**	**16.3**	**12.3**	**13.6**			
	Primary cesarean among nulliparas (%)	73.2	**69.0**	**68.6**	**78.7**	**67.9**	**64.9**	**76.7**	**71.5**	**73.1**	**80.8**	***	**	**
Birthweight	Mean g (SD)	2,408 (613)	**2,395 (615)**	**2,395 (616)**	**2,431 (610)**	**2,372 (618)**	**2,417 (589)**	**2,409 (608)**	**2,446 (606)**	**2,368 (646)**	**2,455 (611)**	**	**	**
	Very low birthweight (<1,500g, %)	8.1	8.3	8.5	7.6	8.8	6.9	8.4	**7.3**	**10.4**	**6.7**	NS	NS	**
	Low birthweight (<2,500g, %)	51.7	**52.6**	**51.3**	**50.4**	**54.1**	**51.0**	**51.7**	49.1	51.5	49.0	*	*	NS
	Small-for-gestation (Zscore <−1.28, %)	18.7	**19.4**	**19.0**	**17.6**	20.3	18.7	18.7	17.4	19.3	16.4	**	NS	NS

		All Twins				Like Gender Pairs			Unlike Gender Pairs			P Values		
		All Groups	Fertile	Subfertile	IVF	Fertile	Subfertile	IVF	Fertile	Subfertile	IVF	Across Groups		
	N, pregnancies	**10,352**	**6,090**	**724**	**3,538**	**4,150**	**391**	**1,817**	**1,940**	**333**	**1,721**			
	N, infants	**20,703**	**12,179**	**1,448**	**7,076**	**8,300**	**782**	**3,634**	**3,879**	**666**	**3,442**	**All**	**Like**	**Unlike**
	Groups	**All**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**1–2–3**	**4–5–6**	**7–8–9**
	Large-for-gestation (Z-score >1.28, %)	1.3	**1.1**	**1.9**	**1.5**	1.2	1.7	1.5	**1.0**	**2.1**	**1.4**	*	NS	*
Gestation	Mean weeks (SD)	35.6 (3.0)	35.6 (3.1)	35.5 (3.1)	35.6 (2.9)	35.5 (3.1)	35.6 (3.0)	35.5 (3.0)	**35.7 (3.0)**	**35.4 (3.3)**	**35.6 (2.9)**	NS	NS	*
	Early Preterm (<32 weeks, %)	9.1	9.1	9.5	8.9	9.6	8.1	9.6	**8.0**	**11.1**	**8.3**	NS	NS	*
	Preterm (<37 weeks, %)	53.4	53.0	54.8	53.8	53.5	56.0	54.7	52.1	53.3	52.8	NS	NS	NS
Birth Defects	Birth Defects (%)	2.4	2.3	2.1	2.7	2.5	2.1	2.6	**1.8**	**2.1**	**2.8**	NS	NS	*
Gender	Male (%)	50.9	50.8	49.1	51.5	**51.1**	**48.3**	**52.9**	50.0	50.0	50.0	NS	*	NS
Infant Death	Infant (0–364 days, %)	**1.61**	**1.79**	**2.07**	**1.22**	**1.80**	**2.30**	**1.24**	1.78	1.80	1.19	**	*	NS
	Neonatal (0–27 days, %)	**1.42**	**1.54**	**1.93**	**1.12**	**1.61**	**2.30**	**1.16**	1.39	1.50	1.07	*	*	NS
	Postneonatal (28–364 days. %)	0.19	0.25	0.14	0.10	0.18	0.00	0.08	0.39	0.30	0.12	NS	NS	NS

[1]Placental complications includes abruptio placenta placenta previa, and vasa previa;

[2]Vaginal includes VBAC, forceps, and vacuum deliveries Significance across fertility groups, NS=not significant (≥0.05);

*p<0.05;

**p<0.01;

***p<0.0001;

bolded values are significant.

Table 4

Risks of Adverse Pregnancy Outcomes by Maternal Fertility Group and Infant Gender

	Fertility	All Twins			Like Gender			Unlike Gender		
Outcome	**Group**	**%**	**ARR**	**95% CI**	**%**	**ARR**	**95% CI**	**%**	**ARR**	**95% CI**
Pregnancy Outcomes[1]										
Gestational	Fertile	8.1	1.00	Reference	8.3	1.00	Reference	7.6	1.00	Reference
Diabetes[2]	Subfertile	11.6	**1.42**	**1.13, 1.79**	10.0	1.15	0.83, 1.59	13.5	**1.85**	**1.32, 2.61**
	IVF	10.7	**1.23**	**1.06, 1.43**	10.4	1.07	0.92, 1.25	11.0	**1.44**	**1.13, 1.83**
Pregnancy	Fertile	20.5	1.00	Reference	20.1	1.00	Reference	21.4	1.00	Reference
Hypertension[3]	Subfertile	26.7	**1.21**	**1.06, 1.39**	28.4	**1.31**	**1.10, 1.57**	24.6	1.09	0.87, 1.35
	IVF	25.5	**1.15**	**1.06, 1.26**	25.3	**1.16**	**1.04, 1.30**	25.6	1.12	0.98, 1.28
Uterine	Fertile	1.0	1.00	Reference	1.0	1.00	Reference	1.1	1.00	Reference
Bleeding	Subfertile	1.9	**1.92**	**1.06, 3.50**	2.3	**2.59**	**1.21, 5.55**	1.5	1.27	0.48, 3.35
	IVF	2.9	**2.58**	**1.80, 3.69**	2.6	**2.71**	**1.70, 4.31**	3.2	**2.30**	**1.30, 4.07**
Placental	Fertile	3.0	1.00	Reference	3.1	1.00	Reference	2.7	1.00	Reference
Complications	Subfertile	5.9	**2.07**	**1.46, 2.93**	6.1	**2.20**	**1.41, 3.44**	5.7	**2.00**	**1.14, 3.52**
	IVF	5.1	**1.83**	**1.45, 2.31**	5.3	**1.91**	**1.42, 2.57**	4.9	**1.82**	**1.22, 2.70**
Prenatal	Fertile	15.8	1.00	Reference	16.3	1.00	Reference	14.8	1.00	Reference
Hospitalizations	Subfertile	17.4	**1.28**	**1.07, 1.53**	16.1	1.11	0.87, 1.42	18.9	**1.48**	**1.13, 1.92**
	IVF	16.5	**1.24**	**1.11, 1.38**	17.1	1.10	0.98, 1.24	16	**1.30**	**1.09, 1.55**
Primary	Fertile	52.8	1.00	Reference	52.6	1.00	Reference	53.1	1.00	Reference
Cesarean[4]	Subfertile	60.2	**1.12**	**1.05, 1.20**	58.8	**1.12**	**1.03, 1.22**	61.9	**1.13**	**1.03, 1.24**
	IVF	65.4	**1.17**	**1.13, 1.21**	64.2	**1.16**	**1.10, 1.22**	66.7	**1.19**	**1.12, 1.26**
Primary	Fertile	69.0	1.00	Reference	67.9	1.00	Reference	71.5	1.00	Reference
Cesarean (nulliparas)[5]	Subfertile	68.6	1.04	0.94, 1.16	64.9	1.11	0.96, 1.28	73.1	1.00	0.87, 1.15
	IVF	78.7	0.87	0.82, 0.92	76.7	**1.16**	**1.07, 1.26**	80.8	1.07	0.99, 1.16

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

[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. Bolded values indicate ARRs and 95% CIs which are significantly greater than the reference group.

Am J Obstet Gynecol. Author manuscript; available in PMC 2018 September 01.

Table 5

Risks of Adverse Infant Outcomes by Maternal Fertility Group and Infant Gender

	Fertility	All Twins			Like Gender			Unlike Gender		
Outcome	**Group**	**%**	**ARR**	**95% CI**	**%**	**ARR**	**95% CI**	**%**	**ARR**	**95% CI**
Infant Outcomes [1]										
Very Low Birthweight	Fertile	8.3	1.00	Reference	8.8	1.00	Reference	7.3	1.00	Reference
(<1,500g)	Subfertile	8.5	1.30	0.99, 1.69	6.9	1.05	0.73, 1.51	10.4	**1.92**	**1.35, 2.74**
	IVF	7.6	1.18	1.00, 1.38	8.4	1.19	0.98, 1.46	6.7	1.23	0.94, 1.61
Low Birthweight	Fertile	52.6	1.00	Reference	54.1	1.00	Reference	49.2	1.00	Reference
(<2,500g)	Subfertile	51.3	1.05	0.98, 1.12	51.0	1.01	0.92, 1.11	51.7	**1.15**	**1.03, 1.28**
	IVF	50.4	1.04	1.00, 1.08	51.7	1.02	0.97, 1.08	49.0	**1.11**	**1.03, 1.18**
Small for	Fertile	19.4	1.00	Reference	20.3	1.00	Reference	17.4	1.00	Reference
Gestational Age	Subfertile	19.0	1.00	0.87, 1.15	18.7	0.95	0.79, 1.14	19.3	1.10	0.89, 1.35
	IVF	17.6	0.92	0.85, 1.00	18.7	0.94	0.85, 1.04	16.4	0.93	0.81, 1.06
Large for	Fertile	1.1	1.00	Reference	1.2	1.00	Reference	1.0	1.00	Reference
Gestational Age	Subfertile	1.9	1.62	0.98, 2.68	1.7	1.28	0.65, 2.53	2.1	**2.34**	**1.10, 4.95**
	IVF	1.5	1.26	0.90, 1.78	1.5	1.20	0.76, 1.88	1.4	1.50	0.88, 2.57
Very Premature	Fertile	9.1	1.00	Reference	9.6	1.00	Reference	8.0	1.00	Reference
(<32 weeks)	Subfertile	9.5	**1.36**	**1.05, 1.75**	8.1	1.11	0.78, 1.59	11.1	**1.80**	**1.24, 2.63**
	IVF	8.9	**1.28**	**1.09, 1.50**	9.6	1.25	1.02, 1.53	8.3	**1.42**	**1.08, 1.87**
Premature	Fertile	53.0	1.00	Reference	53.4	1.00	Reference	52.2	1.00	Reference
(<37 weeks)	Subfertile	54.8	1.08	1.00, 1.16	56.0	1.09	0.99, 1.20	53.5	1.09	0.97, 1.22
	IVF	53.8	**1.07**	**1.03, 1.12**	54.7	**1.07**	**1.01, 1.14**	52.9	**1.10**	**1.02, 1.18**
Birth Defects	Fertile	2.26	1.00	Reference	2.46	1.00	Reference	1.83	1.00	Reference
	Subfertile	2.07	0.96	0.64, 1.41	2.05	0.86	0.50, 1.47	2.10	1.20	0.66, 2.18
	IVF	2.71	**1.26**	**1.01, 1.59**	2.59	1.14	0.84, 1.54	2.85	**1.52**	**1.06, 2.20**
Neonatal Death	Fertile	1.54	1.00	Reference	1.61	1.00	Reference	1.39	1.00	Reference
(0–27 days)	Subfertile	1.93	**1.89**	**1.06, 3.35**	2.30	**2.03**	**1.06, 3.92**	1.50	1.79	0.68, 4.69
	IVF	1.12	0.95	0.63, 1.42	1.16	0.81	0.49, 1.34	1.07	1.23	0.60, 2.53

	Fertility	All Twins			Like Gender			Unlike Gender		
Outcome	**Group**	**%**	**ARR**	**95% CI**	**%**	**ARR**	**95% CI**	**%**	**ARR**	**95% CI**
Infant Death	Fertile	1.79	1.00	Reference	1.80	1.00	Reference	1.78	1.00	Reference
	Subfertile	2.07	**1.87**	**1.08, 3.26**	2.30	**2.00**	**1.05, 3.84**	1.80	1.71	0.71, 4.16
	IVF	1.22	0.96	0.65, 1.41	1.24	0.88	0.53, 1.44	1.19	1.08	0.56, 2.08

[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.