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Pregnancy and birth outcomes in couples with infertility with and without assisted reproductive technology: with an emphasis on US population-based studies

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Abstract

Infertility, defined as the inability to conceive within 1 year of unprotected intercourse, affects an estimated 80 million individuals worldwide, or 10-15% of couples of reproductive age. Assisted reproductive technology includes all infertility treatments to achieve conception; in vitro fertilization is the process by which an oocyte is fertilized by semen outside the body; non-in vitro fertilization assisted reproductive technology treatments include ovulation induction, artificial insemination, and intrauterine insemination. Use of assisted reproductive technology has risen steadily in the United States during the past 2 decades due to several reasons, including childbearing at older maternal ages and increasing insurance coverage. The number of in vitro fertilization cycles in the United States has nearly doubled from 2000 through 2013 and currently 1.7% of all live births in the United States are the result of this technology. Since the birth of the first child from in vitro fertilization >35 years ago, >5 million babies have been born from in vitro fertilization, half within the past 6 years. It is estimated that 1% of singletons, 19% of twins, and 25% of triplet or higher multiples are due to in vitro fertilization, and 4%, 21%, and 52%, respectively, are due to non-in vitro fertilization assisted reproductive technology. Higher plurality at birth results in a >10-fold increase in the risks for prematurity and low birthweight in twins vs singletons (adjusted odds ratio, 11.84; 95% confidence interval, 10.56–13.27 and adjusted odds ratio, 10.68; 95% confidence interval, 9.45–12.08, respectively). The use of donor oocytes is associated with increased risks for pregnancy-induced hypertension (adjusted odds ratio, 1.43; 95% confidence interval, 1.14–1.78) and prematurity (adjusted odds ratio, 1.43; 95% confidence interval, 1.11–1.83). The use of thawed embryos is associated with higher risks for pregnancy-induced hypertension (adjusted odds ratio, 1.30; 95% confidence interval, 1.08–1.57) and large-for-gestation birthweight (adjusted odds ratio, 1.74; 95% confidence interval, 1.45–2.08). Among singletons, in vitro fertilization is associated with increased risk of severe maternal morbidity compared with fertile deliveries (vaginal: adjusted odds ratio, 2.27; 95% confidence interval, 1.78–2.88; cesarean: adjusted odds ratio, 1.67; 95% confidence interval, 1.40–1.98, respectively) and subfertile deliveries (vaginal: adjusted odds ratio, 1.97; 95% confidence interval, 1.30–3.00; cesarean: adjusted odds ratio, 1.75; 95% confidence interval, 1.30–2.35, respectively). Among twins, cesarean in vitro fertilization deliveries have significantly greater severe maternal morbidity compared to cesarean fertile deliveries (adjusted odds ratio, 1.48; 95% confidence

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interval, 1.14–1.93). Subfertility, with or without in vitro fertilization or non-in vitro fertilization infertility treatments to achieve a pregnancy, is associated with increased risks of adverse maternal and perinatal outcomes. The major risk from in vitro fertilization treatments of multiple births (and the associated excess of perinatal morbidity) has been reduced over time, with fewer and better-quality embryos being transferred.

Keywords

assisted hatching; assisted reproduction; birth defects; donor oocytes; fertile; freezing embryos; fresh embryos; in vitro fertilization; intracytoplasmic sperm injection; low birthweight; maternal and paternal age; pregnancy complications; prematurity; severe maternal morbidity; sibling studies; subfertile

Introduction

Infertility, defined as the inability to conceive within 1 year of unprotected intercourse, affects an estimated 80 million individuals worldwide, or 10-15% of couples of reproductive age.[1–3] In the United States, an estimated 12% of couples have ever sought medical assistance to achieve conception, including medical advice (29%), infertility testing (27%), ovulation drugs (20%), artificial insemination (7.4%), surgery or treatment for blocked tubes (3.2%), and in vitro fertilization (IVF) (3.1%).[3] Assisted reproductive technology (ART) includes all infertility treatments to achieve conception; IVF is the process by which an oocyte is fertilized by semen outside the body; non-IVF ART treatments include ovulation induction, artificial insemination, and intrauterine insemination. IVF represents only a small portion of all infertility treatment used in the United States.

Use of ART has risen steadily in the United States during the past 2 decades due to several reasons, including childbearing at older maternal ages and increasing insurance coverage.[3–7] The number of IVF cycles in the United States has nearly doubled from 2000 through 2013 (from 99,629-190,773), and currently 1.7% of all live births in the United States are the result of this technology.[8–13] Since the birth of the first child from IVF >35 years ago, >5 million babies have been born from IVF–half of them within the past 6 years.[14,15] It is well established that both IVF and subfertility, independent of treatment, are associated with compromised maternal and infant perinatal outcomes.[16–31]

Contributing factors

Older age and delayed childbearing

There has been a long-term trend in delaying childbearing among both men and women, with consequences for fertility and reproductive outcomes, reflecting the increasing use of ART among older women.[32–36] From 1980 through 2015, the percent of all births to women ≥30 years of age has more than doubled (from 19.8-43.8%), and increased >3-fold for women ≥35 years of age (from 4.6-16.3%). For multiple births, this trend is even more dramatic, increasing >2-fold for women ≥30 years of age (from 25.0-56.7%), >4-fold for women ≥35 years of age (from 6.0-24.5%), and >7-fold for women ≥40 years of age (from 0.8-5.0%). Advancing maternal age is a well-established factor for reduced fertility, with

fecundity declining gradually beginning at about age 32 years and more rapidly >37 years of age.[32] Age of the woman is the single most important factor associated with failure to conceive. ART does not overcome the decline in fecundity by age: it has been shown that assisted reproduction can only make up for half of the births lost by postponing attempts of pregnancy from age 30-35 years, and <30% of the loss after postponing from 35-40 years.[37] Older paternal age is associated with decreasing androgen levels, declining semen quality, and alterations in testicular morphology, as well as adverse effects on DNA integrity of sperm and increases in telomere length. Time to pregnancy, defined as the likelihood of conception within a certain time period, has been used as a measure of the severity of subfertility and its effect on a subsequent pregnancy. A study of time to pregnancy with advancing paternal age[33] demonstrated that the decline in fecundity is independent of the effect of the woman's age (Table 1).

Overweight and obesity

In conjunction with the rise in delaying childbearing, the prevalence of overweight and obesity also increased, both in the United States and worldwide. In the United States, two thirds of adult women are overweight or obese,[38] with highest rates among black and Hispanic populations, and lowest rates among Asians. Obesity is associated with impaired fertility, primarily due to disorders of the reproductive hormonal profile.[39–42] Current US estimates indicate that in 2014, 25.6% of women were overweight and 24.8% were obese prior to becoming pregnant.[43] Findings from the Study of Women's Health across the Nation indicate that adolescent obesity is associated with a 3-fold increased risk of lifetime nulliparity and a 4-fold increased risk of lifetime nulligravidity.[44] The endocrine and metabolic environment may influence oocyte quality, and therefore embryo development and subsequent implantation and pregnancy outcome. One possible mechanism for the lower pregnancy rate associated with obesity may be altered receptivity of the uterus, due to disturbed endometrial function.[45,46] Even studies limited to obese women using donor oocytes, eliminating the potential effect of older maternal age and lower quality of the embryos, have reported significantly reduced implantation and pregnancy rates and higher miscarriage rates.[47–49] A national US study of IVF reported reduced clinical pregnancy rate with increasing body mass index with autologous but not donor oocytes, and reduced live birth rate with increasing body mass index regardless of oocyte source and embryo state.[48] These findings are in accord with prior studies showing a progressive decline in pregnancy rates with rising obesity.[45,46,50,51] Studies have also shown a more adverse effect of obesity among younger women undergoing IVF treatment.[48,52,53]

Identifying subfertile populations

The challenge of a contemporary evaluation of birth outcomes after assisted conception in the United States is the lack of national databases. Unlike other countries that track their citizens' health from cradle to grave, the only population-based database in the United States that can be used to monitor health after IVF is the national Society for Assisted Reproductive Technology (SART) Clinic Online Reporting System (CORS). The Fertility Success Rate and Certification Act of 1992, PL 102-493, mandates that all cycles of IVF be federally reported; this is achieved through the SART CORS. Data are collected

and verified by SART and reported to the Centers for Disease Control and Prevention (CDC) as the National Assisted Reproductive Technology Surveillance System (NASS). Both SART and the CDC have research programs based on this national system. States Monitoring Assisted Reproductive Technology (SMART) is a collaborative project between the CDC Division of Reproductive Health and the Connecticut Department of Health, the Florida Department of Health, the Massachusetts Department of Public Health, and the Michigan Department of Community Health.[54] In addition, over the past decade the population-based Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART) conducted a series of analyses of maternal-child health using clinical IVF data from SART CORS longitudinally linked to Massachusetts vital records and administrative data in the Pregnancy to Early Life Longitudinal (PELL) data system, a collaboration of the Massachusetts Department of Public Health, Boston University School of Public Health, and the CDC. Birth and fetal death files linked to the hospital discharge records of mother's delivery and child's birth comprise the core of this data system. Program and state agency data from early intervention; birth defects; Women, Infants, and Children program; newborn hearing screening; substance abuse services; and ART are among the selected data linked to the core PELL data. As part of these studies, a subfertility measure was created through a combination of information from birth certificate checkboxes, diagnosis codes of infertility during hospitalizations, and prior use of IVF, which allowed for identification of women with indicators of subfertility who did not receive IVF treatment for the index delivery.[55]

Although they have acknowledged limitations, including the lack of some confounders, the use of linked health data registries, such as the SART CORS, PELL, SMART, MOSART, and statewide vital records, hospital discharge databases, and birth defects and cancer registries offer numerous advantages over other observational studies.[56–58] Record linkage studies can provide large numbers of treated women (inadequate sample size is the single biggest and most consistent problem in clinical studies), detailed treatment data entered prospectively (prior to knowledge of the outcomes), and comprehensive information on validated outcomes.[59] Using statewide or national databases provides a comprehensive picture of a whole population of women and their births, and loss to follow-up is likely to be minimal. The health data registries in NASS, SMART, and MOSART projects are not purely administrative data (eg, a database for drivers' licenses or voter registration), but created specifically for surveillance and monitoring the health of women and their children. An acknowledged limitation of IVF registers, due to the rapidly changing nature of IVF treatment, may be a delay in obtaining data on new techniques, or even an absence of specific exposures (eg, culture media and laboratory conditions).[60] Analyses from linked health data registry studies provide an important birds-eye view of associations, critical public health insights, and help to identify specific areas in need of further bench-level or clinical research.

Perinatal outcomes by fertility status

Data from MOSART have shown that compared to fertile women, subfertile women with and without IVF treatment had greater risks for preterm birth and low birthweight, and infants of subfertile women had greater risks for perinatal death (Table 2).[61] Among twin births, compared to fertile women, infants of subfertile and IVF-treated women had lower

risks for small-for-gestation birthweights, while infants of subfertile women had greater risks for perinatal death, and infants of IVF-treated women had lower risks.

Multiple births

In 2015, multiple births (twins, triplets, quadruplets, and quintuplets) accounted for 1 in 29 births in the United States, with twins representing 97% of all multiples.[62] From 1980 through 2015, the frequency of twins has risen from 1:52-1:30 births (constant at this level since 2008), and the frequency of triplets and higher-order multiples increased from 1:2,702-1:965 births (peaking at 1:539 births in 2001). The rise in multiple birth rates was associated with the widespread use and increasing availability of fertility therapies and delayed maternal age at childbirth (naturally higher risk of multiples with older maternal age).[63,64] It is estimated that 1% of singletons, 19% of twins, and 25% of triplet and higher-order multiples are due to IVF, and 4% of singletons, 21% of twins, and 52% of triplets and higher-order multiples are due to non-IVF ART.[64] Recent declines in triplet or higher birth rates have been linked to changes in IVF treatment guidelines to transfer fewer embryos and single embryos whenever possible, as well as more preimplantation testing and use of more blastocyst-stage embryos.[9,65] Infants born in twin and triplet or higher deliveries are at higher risk of adverse birth outcomes compared with singletons. On an annual basis, >50% of twins and >90% of triplets are born preterm or low birthweight.[66]

Effect of infertility diagnoses

With the exception of higher rates of multiple births from IVF and non-IVF therapies, research over the past decade has consistently shown that subfertility is the primary etiology of compromised outcomes in IVF and non-IVF births[17,27,28,61,67–72] (Table 3). Analyses from MOSART showed that specific diagnoses had greater risks for prematurity, gestational diabetes, hospital utilization, and primary cesarean delivery.[70,71] Significantly increased risks included gestational diabetes (ovulation disorders: adjusted odds ratio [AOR], 1.80; 95% confidence interval [CI], 1.35–2.41); prematurity (ovulation disorders: AOR, 1.36; 95% CI, 1.08–1.71; other factors: AOR, 1.33; 95% CI, 1.05–1.67); prenatal hospital admissions (endometriosis, tubal and other factors, ovulation disorders, and uterine factors: AORs ranging from 1.66–2.68); and primary cesarean delivery (uterine factors: AOR, 1.96; 95% CI, 1.15–3.36). When pregnancy and birth outcomes are examined by infertility-related diagnoses with and without IVF treatment, and compared to outcomes among fertile women, most women with infertility-related diagnoses experienced significantly higher risks for pregnancy hypertension, gestational diabetes, and prenatal admissions.[67] Women with ovulation disorders, regardless of treatment, had significantly higher risks for gestational diabetes and prenatal admissions. Women with endometriosis, regardless of treatment, had higher risks for prenatal admissions. These findings add further support for the primary role of diagnosis–rather than treatment–in the risk for adverse maternal-child outcomes among couples with infertility.

Analyses from the CDC NASS program showed that a diagnosis of uterine factor was associated with an increased risk of loss in women aged ≤40 years (<30 years: adjusted risk ratio [aRR], 1.24; 95% CI, 1.04–1.48; 30-34 years: aRR, 1.27; 95% CI, 1.17–1.38; 35-37

years: aRR, 1.12; 95% CI, 1.03–1.21; 38-40 years: aRR, 1.08; 95% CI, 1.01–1.17).[73] There was an increased risk of loss in women with diminished ovarian reserve aged 30-34 years (aRR, 1.08; 95% CI, 1.01–1.15) and in women with ovulatory disorders age <35 years (<30 years: aRR, 1.12; 95% CI, 1.05–1.19; 30-34 years: aRR, 1.07; 95% CI, 1.02–1.13). There was an increased risk of loss after frozen embryo transfers vs fresh among women age <38 years, but this remained significant in the subanalysis of similar quality embryos only in women age <30 years (aRR, 1.16; 95% CI, 1.04–1.32).

Effect of specific infertility parameters

In the MOSART analyses only 3 specific IVF treatment effects were found to contribute to excess perinatal morbidity in IVF pregnancies: (1) plurality at birth, (2) plurality at conception, and (3) number of embryos transferred. Through a series of analyses, adjusting for parental demographic characteristics, medical and reproductive history factors, and IVF treatment parameters, it was demonstrated that higher plurality at birth results in a >10-fold increase in the risks for prematurity and low birthweight greater among twins vs singletons (AOR, 11.84; 95% CI, 10.56–13.27 and AOR, 10.68; 95% CI, 9.45–12.08, respectively)[74] (Table 4). Plurality at 6 weeks' gestation greater than plurality at birth (indicating fetal loss) was also associated with greater risks for low birthweight, prematurity, and small-for-gestational-age outcomes in both singleton and twin births.[75–77]

Even when plurality at conception and at birth are the same, the transfer of excess embryos is associated with significantly greater risks of moderate growth restriction in singleton as well as twin births.[78] Factors associated with transferring a higher number of embryos reflect suboptimal maternal conditions such as the use of autologous oocytes in women of older ages, less favorable oocyte or embryo quality, less favorable prognosis, or unsuccessful prior cycles (the use of micromanipulation [intracytoplasmic sperm injection {ICSI} and assisted hatching], embryos that were thawed or cleavage stage).[77] The number of embryos transferred is significantly associated with plurality at 6 weeks' gestation, which in turn is associated with greater risks for prematurity and low birthweight.[77]

In the MOSART analyses, only 2 other IVF treatment parameters had any significant adverse effects when adjusted for number of embryos transferred: the use of donor oocytes and thawed embryos[74] (Table 4). The use of donor vs autologous oocytes was associated with increased risks for pregnancy-induced hypertension (AOR, 1.87; 95% CI, 1.45–2.42), prematurity (AOR, 1.43; 95% CI, 1.11–1.83), and primary cesarean (AOR, 1.43; 95% CI, 1.14–1.78). The use of thawed vs fresh embryos was associated with higher risks for pregnancy-induced hypertension (AOR, 1.30; 95% CI, 1.08–1.57), but lower risks for low birthweight (AOR, 0.79; 95% CI, 0.65–0.96) and small-for-gestational-age birthweight (AOR, 0.38; 95% CI, 0.28–0.53).

Intracytoplasmic sperm injection

ICSI a technique that involves the selection and injection of a single spermatozoon into an oocyte; it is a commonly used procedure in IVF, increasing in the United States from 11% in 1995 to 67% in 2013.[11,79–81] This trend is also evident internationally, with 66% of

cycles using ICSI in 2006, ranging from 56% of cycles in Asia to 96% in the Middle East.[15] The use of ICSI offers hope of genetic parenthood for men with profound oligospermia (low sperm count) and, by means of testicular biopsy and epididymal aspiration, even for men with azoospermia (absence of sperm). There are several theoretical concerns, though, regarding ICSI and the potential risks for the offspring[82–86]: (1) the risks of using sperm that potentially carry genetic abnormalities; (2) the risks of using sperm with structural defects; (3) the potential for mechanical and biochemical damage and of introducing foreign material into the oocyte; and (4) the risks associated with circumventing natural selection by injecting a single spermatozoon. The analyses of the outcomes of children born after ICSI have shown mixed results, ranging from a 3-fold increased risk of congenital heart defects,[87] a 2-fold risk of major birth defects, and a 50% increased risk of minor birth defects,[30,88–93] to no difference.[94–98] An analysis from the CDC NASS program evaluated the use and outcomes of ICSI among couples with and without male factor infertility from 1996 through 2012.[99] This study reported the increasing use of ICSI with and without male factor infertility from 76.3-93.3% and from 15.4-66.9%, respectively. The use of ICSI was associated with nonmale factor infertility indications, including unexplained infertility, maternal age ≥38 years, low oocyte yield, having ≥2 prior IVF cycles resulting in no prior live births, and use of preimplantation genetic testing. For cycles with a male factor infertility diagnosis, ICSI use was associated with reduced rates of implantation and multiple births, compared with conventional IVF. However, rates of pregnancy, miscarriage, and live birth were not different for cycles using ICSI vs conventional IVF. For cycles without male factor infertility, ICSI use was associated with decreased rates of implantation, pregnancy, live birth, and multiple live births compared with conventional IVF. Overall, use of ICSI did not improve reproductive outcomes, regardless of whether male factor infertility was present.

Assisted hatching and monozygotic twinning

The risk of monozygotic twinning has been shown to be increased with the use of assisted hatching, the technique of breaking the zona pellucida to facilitate embryo development.[100,101] In a national study of 197,327 pregnancies (including 2824 with evidence of monozygosity) from cycles reported to the SART CORS from 2004 through 2010, the risk of monozygosity was increased with ovulation disorders, donor oocytes, gonadotropin-releasing hormone (GnRH)-agonist suppression, assisted hatching, and day 5-6 transfer, and was decreased with higher follicle-stimulating hormone (FSH) doses (≥3000 IU).[100] In the multivariate analysis, the risk of monozygosity was increased with GnRH suppression and assisted hatching, and decreased with ICSI and higher FSH dose. The interaction showed that although monozygosity was more likely with day 5-6 embryos, assisted hatching had a minimal nonsignificant effect, whereas in day 2-3 embryos, assisted hatching had a substantial statistically significant effect. The risk of monozygosity was higher with fresh day 5-6 embryos, donor oocytes, GnRH-agonist suppression, lower FSH doses, and assisted hatching (particularly with day 2-3 embryos). Compared to day 2-3 embryos, assisted hatching increased the risk of monozygosity in day 2-3 embryos (AOR, 2.47; 95% CI, 2.07–2.94), but day 5-6 embryos were at greater risk both without assisted

hatching (AOR, 3.36; 95% CI, 2.92–3.87) and with assisted hatching (AOR, 3.29; 95% CI, 2.71–3.99).

Use of fresh vs frozen embryos

The use of frozen embryo transfer has increased by >80% since 2006 due to better cryopreservation techniques, improved live birth rates, lower risk of ectopic pregnancies, and more physiologically normal hormonal and endometrial environments.[102–107] Results indicate that singletons born after frozen embryo transfer have comparable or lower risks for low birthweight, small-for-gestational-age birthweight, and preterm birth compared to singletons born after fresh IVF and ICSI, but worse outcomes compared to singletons born after spontaneous conception, including an excess of large-for-gestational-age (LGA) birthweights, pregnancy-induced hypertension, and placenta accreta.[21,24,74,108–113] Belva et al[110] reported rates of major malformations to be highest in children born from cryopreserved embryos with ICSI (6.4%) compared to children born from cryopreserved embryos with IVF (3.1%), and fresh embryos with ICSI (3.4%). Other studies have reported malformation rates in frozen cycles ranging from 1.0%[114] to 8.7%.[115]

Severe maternal morbidity

Several studies have evaluated the risk of severe maternal morbidity (SMM) among subfertile women, with and without IVF treatment.[116–118] An analysis from MOSART of all Massachusetts births from 2004 through 2010 reported a prevalence of SMM among this population (n = 5,458,918) of 1.16%. The overall, crude prevalence of SMM among fertile, subfertile, and IVF deliveries was 1.09%, 1.44%, and 3.14%, respectively. The most common indicator of SMM was blood transfusion. In multivariable analyses, among singletons, IVF was associated with increased odds of SMM compared with both fertile (vaginal: AOR, 2.27; 95% CI, 1.78–2.88; cesarean: AOR, 1.67; 95% CI, 1.40–1.98, respectively) and subfertile (vaginal: AOR, 1.97; 95% CI, 1.30–3.00; cesarean: AOR, 1.75; 95% CI, 1.30–2.35, respectively) deliveries. Among twins, only cesarean IVF deliveries had significantly greater SMM compared with cesarean fertile deliveries (AOR, 1.48; 95% CI, 1.14–1.93). Women who conceive through IVF may have elevated risk of SMM at delivery, largely indicated by blood transfusion, even when compared with a subfertile population.

In an analysis from the CDC NASS group, deliveries were identified in the 2008 through 2012 Truven Health MarketScan Commercial Claims and Encounters Databases.[117] SMM was identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes and *Current Procedural Terminology* codes. Rate of SMM was calculated for IVF and non-IVF pregnancies. Multivariable logistic regression was performed, controlling for maternal characteristics, to calculate AOR and 95% CI for severe morbidity. Of 1,016,618 deliveries, 14,761 (1.5%) were identified as pregnancies conceived with IVF. Blood transfusion was the most common severe morbidity indicator for IVF and non-IVF pregnancies. For every 10,000 singleton deliveries, there were 273 IVF deliveries or postpartum hospitalizations with SMM compared with 126 for non-IVF ($P <$ .001). For IVF singleton deliveries, the rate of severe morbidity decreased from 369 per 10,000 deliveries in 2008 to 219 per 10,000 deliveries in 2012 ($P = .025$). Odds of severe

morbidity were increased for IVF compared with non-IVF singletons (AOR, 1.84; 95% CI, 1.63–2.08). Among multiple gestations, there was no significant difference between IVF and non-IVF pregnancies (rate of severe morbidity for IVF 604/10,000 and non-IVF 539/10,000 deliveries, $P = .089$; AOR, 1.04; 95% CI, 0.91–1.20). Singleton pregnancies conceived with IVF are at increased risk for SMM; however, the rate has been decreasing since 2008. Multiple gestations have increased risk regardless of IVF status.

Wang et al[118] evaluated the risk of SMM at a single academic medical center among 6543 live births in 2012 by mode of conception: IVF, non-IVF infertility treatment (NIFT), and spontaneous conceptions. These investigators defined SMM within 5 categories: obstetrical hemorrhage, placental hemorrhage, hypertensive disorders, cardiovascular disease, and other. The rate of SMM was 1.1% (69/6543, including 7 IVF, 3 NIFT, and 59 spontaneous). Any infertility treatment (IVF + NIFT) was associated with an increased risk of SMM (odds ratio, 2.40; 95% CI, 1.10–5.23). Among singletons, the association between any infertility treatment (IVF + NIFT) and SMM was not statistically significant (odds ratio, 2.11; 95% CI, 0.83–5.37).

Birth defects

Both the SMART program and MOSART evaluated the risks of registry-confirmed birth defects among children conceived with IVF. The CDC used NASS data linked with information from vital records and birth defects registries for 3 states (Florida, Massachusetts, and Michigan).[119] In their study of >4 million infants, they found that singleton infants conceived using IVF were 40% more likely to have a nonchromosomal birth defect (eg, cleft lip and/or palate or a congenital heart defect) compared with all other singleton births. The prevalence of nonchromosomal birth defects (eg, cleft lip and/or palate or congenital heart defects) was slightly increased for women with a diagnosis of ovulation disorder (eg, polycystic ovary syndrome) and when assisted hatching was used. The MOSART analysis, which was based on births to Massachusetts residents from 2004 through 2008, reported a prevalence of cardiac defects of 82 per 10,000 among IVF deliveries compared to 52 per 10,000 among spontaneous conceptions (prevalence ratio, 1.60; 95% CI, 1.30–1.96).[120] The prevalence of noncardiac defects was 180 per 10,000 among IVF deliveries compared to 130 per 10,000 among spontaneous conceptions (prevalence ratio, 1.33; 95% CI, 1.16–1.52). Preliminary analyses of specific defects suggested elevated rates of tetralogy of Fallot, hypoplastic left heart syndrome, esophageal atresia, and rectal and large intestinal atresia among IVF deliveries.

Sibling studies and the effect of changing fertility status

The challenge in studying pregnancy outcomes in women treated for infertility is the choice of an appropriate comparison group. Most studies compared women treated with infertility to fertile women, but this approach has limitations: the 2 groups differ by important characteristics, such as age, socioeconomic status, education, and reproductive history. Several studies used siblings (either conceived spontaneously or with infertility treatment) as the comparison group.[26,69,108,111,121,122] Comparisons within families have the advantage of eliminating the fixed characteristics of the parents (mainly the genetic contribution), which

may affect outcome. In addition, the woman is her own control, adjusting for her change in age, parity, and method of conception, if appropriate.

Data from MOSART of 2 consecutive singleton births from 2004 through 2010 evaluated the effect of changing maternal fertility status.[121] Women were classified as IVF (A), subfertile (S), or fertile (F), and categorized by their fertility status in each birth as A-A, A-S, S-S, F-A, F-S, and F-F. Birthweights in second pregnancies averaged 74-155 g higher, except for births to F-A women, who averaged −16 g lower. Most women had a reduction in length of gestation in their second pregnancies, with F-Awomen having the largest decline (−0.5 weeks). In first birth models, the risks for low birthweight and placental complications were increased for subfertile women (AOR, 1.39; 95% CI, 1.07–1.81 and AOR, 1.97; 95% CI, 1.33–2.93, respectively) and IVF women (AOR, 1.58; 95% CI, 1.29–1.93 and AOR, 3.40; 95% CI, 2.64–4.37, respectively). Second birth models showed increased risks for IVF births of low birthweight (AOR, 3.13; 95% CI, 2.19–4.48) and placental complications (AOR, 2.45; 95% CI, 1.56–3.86) and greater risks of preterm birth for both IVF women (AOR, 2.37; 95% CI, 1.74–3.23) and subfertile women (AOR, 1.47; 95% CI, 1.02–2.13). Declining fertility status, with and without IVF treatment, is associated with increasing risks for adverse outcomes, greatest for women whose fertility status declined the most.

Pairs of singleton births conceived with IVF and born from 2004 through 2013 were identified from SART CORS, matched for embryo stage (blastocyst vs nonblastocyst) and infant gender, categorized by embryo state (fresh vs frozen) in first and second births (4 groups).[108] The data included 7795 singleton pairs. Birthweight z-scores were 0.00-0.04 and 0.24-0.26 in first and second births in fresh cycles, and 0.25-0.34 and 0.50-0.55 in frozen cycles, respectively. LGA was 9.2-9.8% and 14.2-15.4% in first and second births in fresh cycles, and 13.1-15.8% and 20.8-21.0% in first and second births in frozen cycles. The risk of LGA was increased in frozen cycles (first births: AOR, 1.74; 95% CI, 1.45–2.08; and in second births when the first birth was not LGA: AOR, 1.70; 95% CI, 1.46–1.98 for fresh/frozen and AOR, 1.40; 95% CI, 1.11–1.78 for frozen/frozen). These results with siblings indicate that frozen embryo state is associated with an increased risk for LGA. The implications of these findings for childhood health and risk of obesity are unclear, and warrant further investigation.

Conclusions

Subfertility, with or without IVF or NIFT to achieve a pregnancy, is associated with increased risks of adverse maternal and perinatal outcomes. The major risk from IVF treatments of multiple births (and the associated excess of perinatal morbidity) has been reduced over time, with fewer and better-quality embryos transferred.

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TABLE 1

Time to pregnancy by age

Gender	Age, y	Time to pregnancy, mo (95% CI)	*P* value
Women	≤25	5.0 (3.7–6.4)	.04
	>25–30	5.9 (4.8–6.9)	
	>30–35	7.5 (6.1–8.8)	
	>35	9.5 (6.8–12.1)	
Men	≤25	7.0 (5.1–8.9)	<.001
	>25–30	6.9 (5.6–8.2)	
	>30–35	9.3 (7.9–10.7)	
	>35–40	11.4 (9.5–13.4)	
	>40–45	12.4 (8.6–16.2)	
	>45	37.2 (27.1–47.3)	
Men with women <25 y			
	>25–30	6.2 (4.3–8.0)	<.001
	>30–35	6.0 (2.8–9.1)	
	>35–40	11.5 (7.3–15.7)	
	>40	23.2 (14.5–31.9)	

Adapted.[33]

Models adjusted for age of other partner; women's weight, body mass index, smoking, alcohol consumption, tea and coffee intake, parity, contraceptive use, menstrual pattern, and age at menarche; and men's smoking, alcohol consumption, coital frequency, and living standard. Also excluded women with gynecologic history, other risk factors for subfertility, or conceived after treatment.

CI, confidence interval.

TABLE 2

Perinatal outcomes by maternal fertility status and plurality, 2004 through 2008, live births and fetal deaths in Massachusetts

			Fertile as reference		Subfertile as reference	
		%	AOR	95% CI	AOR	95% CI
Singletons						
Preterm	Fertile	6.4	1.00	Reference	0.80[a]	0.72–0.89[a]
	Subfertile	8.1	1.24[a]	1.12–1.38[a]	1.00	Reference
	IVF	10.2	1.53[a]	1.40–1.67[a]	1.23[a]	1.08–1.41[a]
Low birthweight	Fertile	5.4	1.00	Reference	0.83[a]	0.74–0.94[a]
	Subfertile	5.7	1.20[a]	1.06–1.36[a]	1.00	Reference
	IVF	7.8	1.51[a]	1.37–1.67[a]	1.26[a]	1.08–1.47[a]
Small for gestational age	Fertile	8.1	1.00	Reference	1.05	0.94–1.17
	Subfertile	6.5	0.95	0.85–1.06	1.00	Reference
	IVF	8.1	1.05	0.96–1.16	1.10	0.96–1.27
Perinatal death	Fertile	0.43	1.00	Reference	0.66[a]	0.46–0.95[a]
	Subfertile	0.58	1.51[a]	1.05–2.17[a]	1.00	Reference
	IVF	0.42	1.00	0.67–1.50	0.66	0.40–1.11
Twins						
Preterm	Fertile	53.0	1.00	Reference	0.74	0.31–1.76
	Subfertile	56.5	1.35	0.57–3.20	1.00	Reference
	IVF	53.8	0.89	0.68–1.18	0.66	0.23–1.90

			Fertile as reference		Subfertile as reference	
		%	AOR	95% CI	AOR	95% CI
Low birthweight	Fertile	53.0	1.00	Reference	0.99	0.83–1.18
	Subfertile	50.5	1.01	0.85–1.20	1.00	Reference
	IVF	50.3	0.98	0.89–1.09	0.98	0.82–1.17
Small for gestational age	Fertile	20.6	1.00	Reference	1.25[a]	1.02–1.52[a]
	Subfertile	16.9	0.80[a]	0.66–0.98[a]	1.00	Reference
	IVF	17.9	0.85[a]	0.75–0.96[a]	1.06	0.86–1.30
Perinatal death	Fertile	2.57	1.00	Reference	0.27[a]	0.17–0.42[a]
	Subfertile	6.15	3.73[a]	2.37–5.87[a]	1.00	Reference
	IVF	1.15	0.55[a]	0.34–0.89[a]	0.15[a]	0.09–0.25[a]

Adapted.[61]

Models adjusted for maternal age, race/ethnicity, marital status, education, payer status, smoking, prenatal care, preexisting conditions (diabetes mellitus and chronic hypertension), parity, and infant sex. Sample based on live births for preterm birth, low birthweight, and small for gestational age; sample based on live births and fetal deaths for perinatal death.

AOR, adjusted odds ratio; *CI*, confidence interval; *IVF*, in vitro fertilization.

[a]Significantly different than reference group.

TABLE 3

Adverse pregnancy outcomes by infertility diagnosis and maternal fertility status, 2004 through 2008, live births in Massachusetts

	Fertile (reference)		Male factor			Endometriosis						Ovulation disorders						Tubal factors			Inflammation		
	No ART		IVF			IVF			No IVF			IVF			No IVF			IVF			No IVF		
Outcomes[a]	%	AOR	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI	%	AOR	95% CI
Pregnancy hypertension	8.4	1.00	15.2	1.42[c]	1.23–1.63[c]	11.8	0.90	0.64–1.26	11.0	1.24	0.94–1.63	18.3	1.53[c]	1.23–1.91[c]	11.9	1.09	0.83–1.42	13.9	1.08	0.84–1.38	8.2	0.98	0.84–1.14
Gestational diabetes	5.5	1.00	7.5	1.15	0.96–1.38	6.4	0.93	0.62–1.39	6.4	1.08	0.75–1.57	14.2	2.17[c]	1.72–2.73[c]	10.8	1.94[c]	1.52–2.48[c]	10.8	1.42	1.09–1.84	4.8	0.88	0.73–1.06
Prenatal Hospitalizations																							
Emergency room visits	22.1	1.00	13.4	0.89	0.78–1.03	14.5	1.08	0.80–1.44	48.0	3.38[c]	2.85–4.01[c]	14.8	1.01	0.80–1.26	49.6	2.80[c]	2.42–3.23[c]	18.0	1.05	0.85–1.28	60.5	3.42[c]	3.15–3.71[c]
Observational stays	12.5	1.00	14.1	1.12	0.97–1.28	15.5	1.30	0.99–1.71	23.6	2.02[c]	1.67–2.46[c]	15.4	1.20	0.96–1.49	24.0	1.92[c]	1.62–2.27[c]	13.9	1.07	0.86–1.34	27.3	2.25[c]	2.06–2.46[c]
Hospital admissions	3.8	1.00	6.3	1.18	0.97–1.43	10.1	1.97[c]	1.38–2.80[c]	11.9	3.34[c]	2.59–4.31[c]	12.3	2.31[c]	1.81–2.96[c]	11.3	2.56[c]	2.05–3.21[c]	8.6	1.51[c]	1.14–2.01[c]	11.9	2.79[c]	2.47–3.15[c]
Primary cesarean[b]	21.4	1.00	47.8	1.95[c]	1.75–2.17[c]	50.6	2.12[c]	1.67–2.69[c]	34.9	1.93[c]	1.60–2.33[c]	47.3	1.71[c]	1.43–2.04[c]	26.8	1.27[c]	1.07–1.51[c]	46.2	1.88[c]	1.57–2.25[c]	18.7	0.92	0.83–1.02
Preterm birth	6.9	1.00	19.5	1.24[c]	1.07–1.44[c]	20.2	1.22	0.90–1.66	10.9	1.66[c]	1.26–2.18[c]	26.8	1.93[c]	1.55–2.41[c]	11.5	1.38[c]	1.10–1.74[c]	21.7	1.47[c]	1.16–1.85[c]	10.4	1.44[c]	1.27–1.65[c]
Low birthweight	6.0	1.00	20.6	1.27[c]	1.08–1.48[c]	19.0	0.97	0.70–1.33	8.3	1.46[c]	1.07–1.99[c]	25.0	1.60[c]	1.23–2.06[c]	10.6	1.38[c]	1.09–1.76[c]	22.1	1.42[c]	1.11–1.82[c]	10.1	1.54[c]	1.34–1.76[c]
Small for gestational age	8.3	1.00	13.5	1.06	0.91–1.23	13.6	1.05	0.77–1.43	9.2	1.08	0.81–1.43	14.1	1.04	0.82–1.32	10.9	1.16	0.93–1.46	12.5	0.97	0.77–1.24	11.3	1.27[c]	1.12–1.44[c]

Adapted.[70]

AOR, adjusted odds ratio; *ART*, assisted reproductive technology; *CI*, confidence interval; *IVF*, in vitro fertilization.

[a]Models adjusted for maternal age, race/ethnicity, education, preexisting medical conditions (chronic hypertension and diabetes), and plurality;

[b]Models adjusted for all factors in model a, plus breech/malpresentation and cephalopelvic disproportion and excluding women with prior cesarean delivery;

[c]Significantly different than reference group.

TABLE 4

Risks of adverse pregnancy and birth outcomes by plurality at birth and assisted reproductive technology treatment parameters, 2004 through 2008, live births in Massachusetts

		Maternal outcomes						Infant outcomes									
		Pregnancy hypertension		Gestational diabetes		Primary cesarean[b]		Prematurity		Low birthweight		Small for gestational age		Large for gestational age		Birth defects	
Or other factor	Categories	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Plurality at birth	Single	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Twin[a]	2.58[d]	2.27–2.94[d]	1.30[d]	1.10–1.54[d]	5.83[d]	5.17–6.57[d]	11.84[d]	10.56–13.27[d]	10.68[d]	9.45–12.08[d]	2.17[d]	1.86–2.53[d]	0.19[d]	0.12–0.31[d]	2.54[d]	1.96–3.28[d]
	Twin[b]	–	–	–	–	4.29[d]	3.36–5.48[d]	7.51[d]	5.84–9.65[d]	6.42[d]	4.86–8.48[d]	1.58[d]	1.14–2.19[d]	0.21[d]	0.14–0.33[d,d]	1.87[d]	1.06–3.32[d]
Gestational	No	–	–	–	–	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Diabetes	Yes[c]	–	–	–	–	1.22[d]	1.00–1.50[d]	1.19	0.97–1.46	1.11	0.89–1.37	0.91	0.69–1.19	1.40[d]	1.07–1.82[d]	1.50[d]	1.00–2.25[d]
Pregnancy	No	–	–	–	–	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Hypertension	Yes[c]	–	–	–	–	1.86[d]	1.58–2.18[d]	2.70[d]	2.32–3.15[d]	1.83[d]	1.56–2.14[d]	1.16	0.94–1.43	1.17	0.92–1.48	1.06	0.74–1.52
Oocyte	Autologous	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Source	Donor	1.87[d]	1.45–2.42[d]	1.24	0.89–1.72	1.43[d]	1.14–1.78[d]	1.43[d]	1.11–1.83[d]	1.24	0.95–1.62	0.90	0.64–1.27	1.04	0.68–1.61	1.12	0.64–1.98
Semen	Autologous	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Source	Donor	1.28	0.85–1.95	0.85	0.47–1.52	1.12	0.80–1.59	0.77	0.51–1.17	0.63	0.39–1.01	0.64	0.34–1.19	1.12	0.66–1.91	0.75	0.27–2.06
ICSI	No	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Yes	0.91	0.78–1.06	1.07	0.89–1.29	1.04	0.92–1.17	0.92	0.80–1.05	0.95	0.82–1.10	1.20[d]	1.00–1.43[d]	1.14	0.92–1.41	0.78	0.57–1.06

Or other factor	Categories	Maternal outcomes						Infant outcomes									
		Pregnancy hypertension		Gestational diabetes		Primary cesarean[b]		Prematurity		Low birthweight		Small for gestational age		Large for gestational age		Birth defects	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Assisted	No	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Hatching	Yes	0.92	0.80–1.07	0.96	0.80–1.15	1.01	0.90–1.13	1.01	0.88–1.15	0.95	0.83–1.10	1.01	0.85–1.21	0.91	0.74–1.12	0.93	0.69–1.26
Embryo	Fresh	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
State	Thawed	1.30[d]	1.08–1.57[d]	0.99	0.78–1.25	1.06	0.91–1.23	1.12	0.94–1.33	0.79[d]	0.65–0.96[d]	0.38[d]	0.28–0.53[d]	1.10	0.43–2.84	0.94	0.63–1.40
Embryos	1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Transferred	2	1.04	0.83–1.31	1.01	0.78–1.32	1.03	0.88–1.21	1.05	0.85–1.30	1.12	0.87–1.45	1.06	0.81–1.40	1.20	0.91–1.57	1.30	0.77–2.18
	≥3	1.11	0.86–1.43	1.01	0.75–1.35	1.13	0.94–1.35	1.15	0.91–1.45	1.21	0.92–1.60	1.08	0.80–1.46	1.17	0.86–1.60	1.32	0.75–2.31
Fetal	1	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Heartbeats	2	0.94	0.69–1.27	1.33	0.97–1.82	1.01	0.82–1.24	1.49[d]	1.16–1.91[d]	1.57[d]	1.19–2.08[d]	1.32	0.96–1.82	0.78	0.54–1.12	1.42	0.81–2.51
	≥3	0.97	0.60–1.58	1.25	0.68–2.30	1.38	0.89–2.16	2.07[d]	1.39–3.09[d]	2.30[d]	1.52–3.49[d]	2.04[d]	1.25–3.34[d]	0.61	0.22–1.71	1.55	0.64–3.75

Adapted.[74]

CI, confidence interval; *ICSI*, intracytoplasmic sperm injection; *OR*, odds ratio.

[a]Models are adjusted for maternal and paternal age, race and ethnicity, and education; diagnoses; maternal preexisting medical conditions (chronic hypertension and other diabetes); plurality at 6 wk' gestation and at birth; oocyte source; semen source; ICSI; assisted hatching; embryo state; and number of embryos transferred;

[b]Models adjusted for all factors in model a, plus breech/malpresentation and cephalopelvic disproportion, and excluding women with prior cesarean delivery;

[c]Models adjusted for all factors in model a, plus gestational diabetes and pregnancy hypertension;

[d]Significant adjusted OR and 95% CIs.