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ASSISTED REPRODUCTION TECHNOLOGIES

Risk of prematurity and infant morbidity and mortality by maternal fertility status and plurality

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Abstract

Purpose To evaluate the risk of prematurity and infant mortality by maternal fertility status, and for in vitro fertilization (IVF) pregnancies, by oocyte source and embryo state combinations.

Methods Women in 14 States who had IVF-conceived live births during 2004–13 were linked to their infant's birth and death certificates; a 10:1 sample of non-IVF births was selected for comparison; those with an indication of infertility treatment on the birth certificate were categorized as subfertile, all others were categorized as fertile. Risks were modeled separately for the fertile/subfertile/IVF (autologous-fresh only) group and for the IVF group by oocyte source-embryo state combinations, using logistic regression, and reported as adjusted odds ratios (AORs) and 95% confidence intervals (CI).

Results The study population included 2,474,195 pregnancies. Placental complications (placenta previa, abruptio placenta, and other excessive bleeding) and prematurity were both increased with pregestational and gestational diabetes and hypertension, among subfertile and IVF groups, and in IVF pregnancies using donor oocytes. Both subfertile and IVF pregnancies were at risk for prematurity and NICU admission; IVF infants were also at risk for small-for-gestation birthweight, and subfertile infants had greater risks for neonatal and infant death. Within the IVF group, pregnancies with donor oocytes and/or thawed embryos were at greater risk of large-for-gestation birthweight, and pregnancies with thawed embryos were at greater risk of neonatal and infant death.

Conclusions Prematurity was associated with placental complications, diabetes and hypertension, subfertility and IVF groups, and in IVF pregnancies, donor oocytes and/or thawed embryos.

Keywords Embryo state · Fertility status · Infant morbidity · Infant mortality · Oocyte source · Placental complications · Prematurity

Introduction

In 2015 in the USA, there were nearly 73,000 babies born from in vitro fertilization (IVF), accounting for 1.8% of all births, a proportion which has doubled since 2000 [1–4]. It is well-established that both assisted reproductive technology (ART) and subfertility, independent of treatment, are associated with compromised maternal and infant perinatal outcomes [5–12]. A persistent and unresolved issue is how much of this excess risk is due to the biology of the subfertile couple

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versus the ART treatments used to achieve a live birth [13–17]. The purpose of this analysis is to evaluate the risk of prematurity and infant morbidity and mortality for singletons and twins by maternal fertility status, and for IVF pregnancies, by oocyte source and embryo state combinations.

Materials and methods

This study involved linking data from the national IVF database, the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS), to birth certificates as part of a larger study in 14 States on assisted reproductive technology (ART) and risk of childhood cancer (NIH grant R01 CA151973). The data for this analysis was limited to live births (≥ 22 weeks' gestation and ≥ 300 g birthweight). Two comparison groups were identified. First, women classified as fertile, subfertile, and IVF-treated (limited to autologous oocytes-fresh embryos [autologous-fresh]) were compared, with fertile women as the reference group (fertile and subfertile are defined in the birth certificate section below). Second, within the IVF-treated population, women were categorized by oocyte source-embryo state combinations (autologous-fresh, autologous-thawed, donor-fresh, and donor-thawed) used in their IVF cycle, with women using autologous-fresh cycles as the reference group.

SART CORS data

The Society for Assisted Reproductive Technology (SART) maintains Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant Business Associate Agreements with its 375 reporting clinics. In 2004, following a contract change with the Centers for Disease Control and Prevention, SART leveraged the SART CORS data system for the purposes of conducting research. The database includes information on demographic factors, IVF diagnoses and treatment parameters, and pregnancy outcomes. The data in the SART CORS are validated annually with some clinics having on-site visits for chart review. During each visit, data reported by the clinic are compared with information recorded in the medical record; most data fields have discrepancy rates less than 2%, with diagnosis fields ranging from 2 to 5% [4].

Birth and death certificate data

Births during the study time period (2004–13) included both the 1989 and 2003 revisions of the US Certificate of Live Birth. Of the 14 States in this study, the 2003 revision was implemented in 2003 (Pennsylvania), 2004 (Florida and New York State), 2005 (Texas), 2006 (California and Ohio), 2007 (Colorado and Michigan), 2008 (New York City), 2010 (Illinois and North Carolina), 2011 (Massachusetts), and 2012 (Virginia); New Jersey and Connecticut implemented the 2003 revision after the study time period (2015 and 2016, respectively). Therefore, data from both the 1989 and 2003 revisions of the birth certificate are included for births in this study. Data from the 1989 revision of the birth certificate included the following placental complications: abruptio placenta: premature separation of a normally implanted placenta from the uterus; placenta previa: implantation of the placenta over or near the internal opening of the cervix; and other excessive bleeding: the loss of a significant amount of blood from conditions other than abruptio placenta or placenta previa. In the 2003 revision of the birth certificate, three checkboxes were added to indicate that (1) *the pregnancy resulted from infertility treatment*, (*worded as: if yes, check all that apply*): (2) *Fertility-enhancing drugs, artificial insemination, or intrauterine insemination*; (3) *Assisted reproductive technology* (e.g., *IVF* [in vitro *fertilization*], *GIFT* [*gamete intrafallopian transfer*]). Pregnancies which linked to the SART CORS cycles were categorized as IVF; pregnancies with an indication that it resulted from infertility treatment (via the infertility checkbox) but did not link to an IVF cycle were categorized as subfertile; the remaining pregnancies were categorized as fertile. Known limitations of birth certificate data include the unreliability of selected items (such as maternal weight gain), the high rate of missing values for other items (such as father's age and race/ethnicity, maternal height and prepregnancy weight) [1]. The validity of the 1989 and 2003 revisions of the birth certificate data using the medical record as the gold standard has been assessed, with most items reported accurately, with high specificity and wide variance in sensitivity, reflecting that if a rare condition was present, it often was not documented, but if the condition was documented, it was likely that it was present [18–27]. All States routinely link infant death certificates to their corresponding birth certificates for legal and statistical purposes. When the birth and death of an infant occur in different States, copies of the records are exchanged by the State of death and State of birth in order to affect a link. In addition, if a third State is identified as the State of residence at the time of birth or death that State is also sent a copy of the appropriate certificate by the State where the birth or death occurred. Infant deaths were classified by age at occurrence as neonatal (birth to 27 days), postneonatal (28–364 days), and infant (birth to 364 days). Cause of death, based on International Classification of Diseases, Tenth Revision (ICD-10) was summarized, and the leading ten causes by plurality and age at death (neonatal, postneonatal, and infant mortality) compared with national statistics for the United States [28].

Linkage procedure

In the course of conducting a study on childhood cancer following IVF, we linked the SART CORS data and State Vital Records. Each State received a file of cycles of women who were residents of that State. To begin the linkage process, a limited data file was generated by Redshift Technologies, Inc., the organization which maintains the SART CORS on behalf of SART, containing only the following factors: study-specific patient ID and cycle ID, woman's first, middle name or initial, and last names, social security number, date of birth, zip code of residence, date of cycle outcome (live birth), plurality of the live birth, gender(s) and birthweight(s) of the infant(s). The State then performed a linkage to identify the IVF births; 91% of IVF-conceived births in the SART CORS were linked to their respective birth certificates. For each delivery identified as having been conceived by IVF, we requested that the subsequent 10 deliveries (all liveborn infants from a pregnancy) be selected as the non-IVF comparison group, although not all States implemented this request, providing the next 10 births (individual children) instead, and often only one infant from a twin or triplet + birth. The files of the study children were then linked to each State's vital records (death certificates). Once all data was linked and complete, the files were stripped of all identifying elements (such as names, dates, social security numbers, and any other information that could identify an individual), but retaining the patient ID and cycle ID for the IVF group. The de-identified files were then transmitted to the investigators using secure file transfer methods. For the investigators, Redshift created a de-identified data file with the study-specific patient ID and cycle ID, and the IVF treatment parameters, and sent the file by secure file transfer methods. We then merged the two de-identified data files using the patient ID and cycle ID. This study was approved by the Institutional Review Boards at Michigan State University, the University of Michigan, the University of Minnesota, and each of the State Departments of Health.

The data files received from the States were indexed by infant. However, in this study, the analysis was by mother. Although the family structure (identification of siblings) could be reliably determined for the IVF infants, this was not true for the controls, as discussed above. Therefore, each record of a multiple birth was weighted by 1/plurality; i.e., if the birth was recorded as a twin, each record would receive the weight of ½. Summing the two records in the same family using this weight would then estimate the mother's outcome correctly. Since some States enumerated all infants from the same birth in the comparison group, while other States sampled births rather than deliveries, the weighting would underestimate the number of mothers of multiples (i.e., will be conservative with respect to any statistical test). The standard deviations reported were not weighted, since weighting reduces the estimate of the standard deviation.

Variables

Independent variables included oocyte source-embryo state combinations (autologous-fresh, autologous-thawed, donor-fresh, donor-thawed), maternal age at delivery (continuous and as 18–29, 30–34, 35–37, 38–40, and ≥ 41 years), race (white, black, Asian, other) and Hispanic ethnicity, education (less than 8th grade, some high school, high school graduate or GED, some college or associate degree, bachelor's degree, or post-graduate education), maternal prepregnancy medical conditions (hypertension and diabetes mellitus), and parity (nulliparous, 1, or ≥ 2). IVF treatment parameters included the number of prior IVF cycles, infertility diagnoses (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal factors, uterine factors, other factors, and unexplained), number of embryos transferred (1, 2, > 2), and number of fetal heartbeats at 6 weeks' gestation (1, 2, or > 2). The pregnancy, birth, and infant outcomes included pregnancy complications (gestational diabetes and pregnancy hypertension), placental complications (other excessive bleeding, placenta previa, and abruptio placenta), mode of delivery (vaginal, cesarean, and repeat cesarean), and infant sex; State and year of birth were also included in the models. Dependent variables included preterm birth (very preterm, 22–27 weeks; early preterm, 22–32 weeks; and preterm, 22–36 weeks), very low birthweight (< 1500 g), low birthweight (< 2500 g), small-for-gestation birthweight (SGA, birthweight z-score ≤ −1.28), large-for-gestation birthweight (LGA, birthweight z-score ≥ 1.28), neonatal intensive care unit (NICU) admission, neonatal death (days 0–27 of life), postneonatal death (28–364 days), and infant death (days 0–364), as well as the placental complications. Birthweight z-scores were calculated using gender-specific national standards [29] as recommended by Land [30], with z-scores ≤ − 1.28 reflecting birthweight below the 10th percentile for gestation, and z-scores ≥ 1.28 indicating birthweight above the 90th percentile for gestation.

Statistical methods

We modeled the risk of placental complications (placenta previa, abruptio placenta, and other excessive bleeding) by diabetes and hypertension (pregestational and gestational), and fertility group and IVF group, separately by plurality. We modeled the risks of very early preterm birth, early preterm birth, preterm birth, SGA, LGA, NICU admission,

neonatal death and infant death by fertility group and IVF group, by diabetes and hypertension, and placental complications, separately by plurality. The fertility group included the fertile/subfertile/IVF [autologous-fresh only] study population (pregnancies to fertile women were the reference group) (model 1), and the within IVF study population (autologous-fresh/autologous-thawed/donor-fresh/donor-thawed; pregnancies to women with autologous-fresh cycles were the reference group) (model 2) using logistic regression as adjusted odds ratios (AOR) and 95% confidence intervals. Models were adjusted for maternal fertility status, age, race and ethnicity, parity, pre-existing conditions (diabetes mellitus and chronic hypertension), pregnancy complications (gestational diabetes and pregnancy hypertension), placental complications (abruptio placenta, placenta previa, and other excessive bleeding), plurality at birth (singleton or twin), mode of delivery, State of residence, year of birth, and infant sex. Models of placental complications by plurality were limited to the preterm birth outcomes, since the other outcomes (SGA, LGA, NICU admission, and neonatal and infant death) were highly correlated with prematurity. We tested interactions and they did not significantly reduce the lack of fit of the models and therefore were not retained. Only models with sufficient sample size are presented in the tables. All analyses were performed using the SAS software, version 9.4 (SAS Institute).

Results

The study population included 2,478,459 pregnancies [2,258,460 fertile, 12,184 subfertile and 140,686 autologous-fresh, 36,509 autologous-thawed, 22,754 donor-fresh and 7866 donor-thawed]; 2,379,210 singleton pregnancies (2,379,210 infants and 9531 deaths), and 94,985 twin pregnancies (189,971 infants and 2903 deaths). A description of maternal characteristics by fertility group and plurality is shown in Table 1. Women in the fertile group were more likely to be younger, Hispanic, multiparous, and less likely to be college graduates compared to the subfertile and IVF groups, which for most characteristics tended to be similar. Within the IVF group, women using their own oocytes (autologous) averaged about 7 years younger than women using donor oocytes. Women with IVF-fresh embryo cycles were most likely to be nulliparous (47.6 to 67.7% of singletons and 24.5 to 34.1% of twins).

The infertility diagnoses and IVF treatment parameters are shown in Table 2. Women with autologous-fresh cycles had fewer prior IVF cycles compared to women with donor or thawed cycles. Male factor infertility was the most common diagnosis in cycles using autologous oocytes (ranging from 39 to 44.1% by plurality), and diminished ovarian reserve was most common in cycles using donor oocytes (ranging from 75.3 to 77.9% by plurality). Only 11.8 to 23.7% of singleton IVF births had a single embryo transferred, 61.1 to 82.8% of twin births had two embryos transferred, indicating probable evidence of fetal loss and embryo splitting.

The pregnancy, birth, and infant outcomes by fertility group and plurality are shown in Table 3. Diabetes and hypertension were more frequent in the subfertile and the donor-fresh and donor-thawed IVF groups, and placental complications generally more common in the IVF donor groups. Prematurity (and associated reduced birthweight) was more likely in the subfertile and IVF donor groups. SGA was lowest and LGA highest in the IVF thawed embryo groups (in both autologous and donor oocytes groups). Neonatal and infant mortality was highest in the subfertile group, followed by the IVF donor-thawed group.

The results of the placental complications models are shown in Table 4. Both pregestational and gestational diabetes were associated with increased risks for placental complications, regardless of plurality (model 1). Within the IVF population (model 2), gestational diabetes was associated with increased risk of abruptio placenta in singletons and placenta previa and other excessive bleeding in twins. Hypertension (both pregestational and gestational) was associated with increased risks of abruptio placenta and other excessive bleeding, regardless of plurality (model 1); the pattern was similar within the IVF population (model 2). Compared to fertile women, both subfertile and IVF-treated women had increased risks for placental complications, highest for placenta previa in the latter group (AOR 3.79, 95% CI 3.48, 4.13 for singletons, and AOR 2.19, 95% CI 2.19, 95% CI 1.63, 2.94 for twins) (model 1). Within the IVF population, the risks for other excessive bleeding were generally increased for pregnancies with donor oocytes and/or thawed embryos, regardless of plurality. Placental complications were, in turn, strongly associated with prematurity (Table 5). The risks with abruptio placenta was increased 10-fold (AOR 9.52, 95% CI 9.07, 9.98) and 7-fold (AOR 7.04, 95% CI 6.09, 8.14), respectively, in models 1 and 2. The pattern for placenta previa (AOR 6.94, 95% CI 6.52, 7.40, and AOR 6.52, 95% CI 5.79, 7.39, respectively, in models 1 and 2) and other excessive bleeding (AOR 1.46, 95% 1.34, 1.58, and AOR 1.35, 95% CI 1.10, 1.65, respectively, in models 1 and 2), showed a similar pattern.

Prematurity was associated with deviations from normal growth (both SGA and LGA birthweights), and greater risks of NICU admission, and death (Tables 5 for singletons and Table 6 for twins). Premature singletons had a 7-fold risk of neonatal death (AOR 7.24, 95% CI 6.61, 7.93 [model 1] and AOR 6.84, 95% CI 4.52, 10.36 [model 2]) and twins had more than a twofold risk (AOR 2.64, 95%

Table 1 Maternal characteristics by fertility group and plurality at birth

Factor	Categories	Singleton births						Twin births					
	Fertility	Fertile	Subfertile	IVF				Fertile	Subfertile	IVF			
	Group			A-fresh	A-thawed	D-fresh	D-thawed			A-fresh	A-thawed	D-fresh	D-thawed
	N, pregnancies	2,223,647	9941	97,852	27,930	13,875	5965	34,033	2032	40,406	8127	8586	1801
Age (years)	Mean (SD)	28.8 (5.9)	33.8 (5.2)	35.0 (4.2)	35.0 (4.2)	42.0 (4.7)	42.5 (5.1)	30.2 (5.9)	34.4 (5.4)	33.8 (4.0)	34.2 (4.0)	41.6 (4.8)	42.2 (5.1)
	(%) 18–29	54.1	20.8	10.4	9.6	1.3	1.5	44.8	16.7	14.0	12.2	1.6	1.7
	30–34	27.6	35.6	34.8	35.6	6.7	6.6	31.3	37.2	41.7	41.5	7.2	6.6
	35–37	10.7	19.8	25.3	27.0	8.3	8.0	13.6	21.3	25.2	25.5	10.0	9.9
	38–40	5.4	13.9	19.7	18.5	15.9	13.3	7.0	12.4	14.9	14.8	16.4	15.2
	≥41	2.2	9.8	9.8	9.3	67.9	70.7	3.3	12.4	4.1	6.0	64.8	66.6
Ethnicity (%)	Hispanic	24.1	8.3	8.2	8.0	7.3	7.4	17.6	7.1	8.8	8.7	8.0	8.1
Race (%)	White	76.2	86.8	82.8	79.8	85.9	85.4	75.6	85.9	84.7	79.9	86.1	85.4
	Black	14.5	4.0	5.0	5.7	4.4	5.0	17.4	4.0	4.6	6.6	4.7	5.3
	Asian	8.8	8.9	11.9	14.3	9.6	9.4	6.5	9.8	10.5	13.4	8.9	9.2
	Other	0.5	0.3	0.3	0.3	0.2	0.2	0.5	0.2	0.3	0.2	0.2	0.1
Parity (%)	Nulliparous (0)	38.6	56.2	67.7	49.0	67.5	47.6	18.1	29.5	34.1	26.8	33.5	24.5
	1	33.0	30.4	23.4	34.6	22.3	35.9	32.1	42.1	40.1	38.6	39.5	36.4
	≥2	28.4	13.4	8.9	16.4	10.2	16.5	49.8	28.4	25.8	34.6	27.0	39.1

Means are weighted, SDs are not weighted

Table 2 Infertility diagnoses and treatment parameters for women in the IVF group by oocyte source and embryo state

		Singleton				Twin			
	N, pregnancies	A-fresh 97,852	A-thawed 27,930	D-fresh 13,875	D-thawed 5965	A-fresh 40,406	A-thawed 8127	D-fresh 8586	D-thawed 1801
Prior IVF	Number of prior cycles (%)	54.5	91.2	66.3	88.7	52.6	90.6	67.1	87.5
	Mean number of cycles (SD)	1.6 (2.2)	2.6 (2.5)	2.4 (2.8)	3.6 (3.4)	1.5 (2.1)	2.4 (2.2)	2.5 (2.8)	3.4 (3.1)
Infertility	Male factor	39.5	39.0	19.0	18.7	41.1	39.0	19.6	19.5
Diagnosis (%)	Endometriosis	11.4	10.8	6.3	6.9	12.1	11.2	6.4	7.5
	Ovulation disorders	16.8	21.2	5.1	6.7	19.3	23.1	5.6	5.7
	Diminished ovarian reserve	14.9	10.2	77.5	76.0	10.5	8.6	77.9	75.3
	Tubal factors	15.9	16.1	6.9	7.6	16.1	16.6	7.1	8.2
	Uterine factors	4.2	4.3	4.6	5.4	3.7	3.6	4.6	5.2
	Other	12.6	13.9	17.8	18.3	11.5	13.3	16.2	17.7
	Unexplained	14.5	13.5	3.4	3.1	14.5	13.4	3.6	3.6
Embryos	1	11.8	23.7	13.3	19.9	0.6	1.5	0.3	1.0
Transferred (%)	2	53.5	51.1	71.3	53.0	64.9	63.8	82.8	61.1
	> 2	34.7	25.2	15.4	27.2	34.5	34.7	16.9	37.9
Fetal heartbeats	1	91.7	93.8	88.8	93.7	0.8	1.0	0.6	1.1
At 6 weeks (%)	2	7.4	5.6	9.9	5.6	93.4	93.5	95.3	93.8
	> 2	0.9	0.6	1.3	0.7	5.8	5.4	4.1	5.0

CI 1.98, 3.53 [model 1] and AOR 2.79, 95% CI 1.93, 4.05 [model 2]). Hypertension was associated with a two- to three-fold risk of prematurity, as well as greater risks of SGA birthweight, and NICU admission. Diabetes was also associated with two- to three-fold risk of prematurity, as well as increased risk of LGA birthweight, and NICU admission. The risks of prematurity and NICU admission were significantly increased for subfertile and IVF-treated women (model 1); SGA birthweight was elevated for infants of IVF women, whereas the risks of neonatal and infant death were increased for infants of subfertile women. Within the IVF group (model 2), prematurity, LGA birthweight, and NICU admission were increased for pregnancies using donor oocytes and/or thawed embryos, and the risks for neonatal or infant death were increased for infants born from thawed embryos.

The ten leading causes of neonatal, postneonatal, and infant mortality by plurality are shown in Table 7; for comparison, national data for 2016 is included [28]. The leading causes of infant mortality among study singletons reflected national rankings, with the number 1 cause being congenital malformations and chromosomal abnormalities (ICD-10 codes Q00-Q99) accounting for 25.4% and 20.8% of deaths, respectively, and the number 2 cause being prematurity and low birthweight (ICD-10 code P07) (10.2% of deaths for study singletons and 17.0% of deaths nationally). This order was reversed for study twins, with prematurity being number 1 cause (19.1% of deaths) and congenital malformations the number 2 cause (13.2% of deaths). Newborns affected by maternal complications of pregnancy (ICD-10 code P01) was the 4th leading cause of death nationally (6.1% of deaths) and for study singletons (3.1% of deaths), and the 3rd leading cause among study twins (9.7% of deaths). Newborns affected by complications of placenta, cord, and membranes (ICD-10 code P02) was the 6th leading cause of death nationally (3.6% of deaths) and for study singletons (2.8% of deaths), and the 7th leading cause among study twins (4.2% of deaths).

Prematurity was the leading cause of neonatal death nationally (25.2% of deaths) and for study twins (22.9% of deaths), and the 2nd leading cause for study singletons (15.7% of deaths). Newborns affected by maternal complications of pregnancy was the 3rd leading cause of neonatal mortality nationally (9.1% of deaths), among study singletons (4.9% of deaths), and study twins (12.2% of deaths). Newborns affected by complications of placenta, cord, and membranes was the 4th, 5th, and 7th leading cause of neonatal mortality nationally (5.4% of deaths), among study singletons (4.4% of deaths) and study twins (5.3% of deaths), respectively.

Congenital malformations and chromosomal abnormalities was the leading cause of postneonatal mortality, accounting for 18.0% of national deaths, 20.8% of deaths among study singletons, and 11.9% of deaths among study twins. Two of the top 10 leading causes of postneonatal mortality reflect the residual adverse effect of prematurity on survival during infancy: chronic respiratory disease originating in the perinatal period (ICD-10 code P27) and

Table 3 Pregnancy, birth, and infant outcomes by maternal fertility group and plurality at birth

		Singleton births						Twin births					
	Fertility group	Fertile	Subfertile	IVF				Fertile	Subfertile	IVF			
	N, pregnancies	2,223,647	9941	A-fresh 97,852	A-thawed 27,930	D-fresh 13,875	D-thawed 5965	34,033	2032	A-fresh 40,406	A-thawed 8127	D-fresh 8586	D-thawed 1801
Factor	Categories												
Diabetes	Pregestational (%)	0.6	0.9	0.7	0.7	0.7	0.9	0.8	1.0	0.6	0.6	0.7	1.0
	Gestational (%)	6.0	9.0	8.7	8.7	10.2	11.0	8.4	9.9	10.6	11.5	12.4	13.0
Hypertension	Pregestational (%)	1.2	2.1	1.6	2.0	3.1	3.3	2.1	2.4	1.7	2.7	3.3	4.6
	Gestational (%)	3.5	6.8	4.4	5.1	9.1	7.9	7.8	12.1	9.1	12.1	18.6	15.8
Placental	Other excessive bleeding (%)	0.8	1.0	1.5	2.4	2.2	1.3	2.7	3.1	3.1	4.5	4.9	5.0
Complications	Placenta previa (%)	0.4	0.9	2.2	1.4	2.2	2.2	0.5	0.9	1.4	1.0	1.6	2.1
	Abruptio placenta (%)	0.5	0.7	0.9	0.6	0.8	0.7	0.8	0.9	1.2	0.8	1.1	0.7
Mode of delivery	Vaginal (%)	67.9	56.3	55.1	46.5	33.4	31.8	26.4	21.7	19.5	17.7	11.9	12.8
	Cesarean (%)	32.1	43.7	44.9	53.5	66.6	68.2	73.6	78.3	80.5	82.3	88.1	87.2
	Repeat cesarean (% of cesarean)	42.7	30.2	22.3	35.2	17.3	37.7	22.0	17.6	12.7	20.5	13.1	26.7
Length of	Mean weeks (SD)	38.7 (2.0)	38.4 (2.4)	38.4 (2.2)	38.4 (2.2)	38.2 (2.4)	38 (2.5)	35.3 (3.2)	34.9 (3.6)	35.3 (3.0)	35.3 (3.0)	35.2 (2.9)	35.1 (2.9)
Gestation	< 28 weeks, %	0.5	1.1	0.7	0.8	0.8	1.1	3.9	5.7	3.3	3.1	2.5	3.0
	< 32 weeks, %	1.1	1.7	1.8	1.6	2.5	2.8	10.5	12.2	10.5	10.9	11.8	11.6
	< 36 weeks, %	6.5	9.0	9.2	8.7	12.1	13.3	43.6	41.6	44.7	45.3	48.2	49.7
	≥ 37 weeks, %	91.9	88.3	88.3	88.9	84.6	82.8	42.0	40.5	41.4	40.6	37.4	35.7
	N, infants (live births)	2,223,647	9941	97,857	27,933	13,876	5966	68,065	4063	80,813	16,253	17,175	3602
	N, infant deaths	8931	64	343	112	49	32	1329	123	1054	181	180	36
Birthweight	Mean grams (SD)	3316 (555)	3268 (632)	3237 (602)	3377 (615)	3243 (643)	3235 (666)	2361 (621)	2302 (671)	2354 (424)	2439 (430)	2356 (411)	2360 (423)
	VLBW, < 1500 g, %	1.0	2.2	1.7	1.5	2.1	2.3	9.5	13.0	9.1	8.0	8.0	8.8
	LBW, < 2500 g, %	6.0	8.9	9.0	6.8	10.7	11.2	54.5	56.2	55.9	49.0	56.8	55.7
	SGA, Z-score ≤ − 1.28, %	8.4	8.6	9.4	5.3	8.2	7.1	21.7	20.8	22.2	15.0	20.2	18.9
	LGA, Z-score ≥ 1.28, %	9.6	9.7	8.7	14.5	11.1	12.8	1.9	2.0	1.5	2.6	1.8	2.0
Gender	Male (%)	51.2	51.3	50.6	51.8	51.2	50.5	50.2	51.7	50.7	50.9	51.3	51.0
NICU	NICU admission (%)	6.0	9.6	7.9	8.3	10.5	10.4	31.2	36.5	32.5	32.3	36.1	36.0
Infant	Infant (0–364 days, %)	0.40	0.64	0.35	0.40	0.35	0.54	1.95	3.03	1.30	1.11	1.05	1.00
Deaths	Neonatal (0–27 days, %)	0.24	0.54	0.25	0.30	0.25	0.35	1.48	2.66	1.02	0.87	0.75	0.83
	Neonatal (% of all deaths)	59.2	84.4	71.7	75.0	69.4	65.6	76.0	87.8	77.9	78.5	71.7	83.3

Table 4 Risk of placental complications by maternal co-morbidities, fertility group, and plurality

Factor	Model	Plurality	Singletons						Twins					
		Outcome	Other		Placenta		Abruptio		Other		Placenta		Abruptio	
			Excessive bleeding		Previa		Placenta		Excessive bleeding		Previa		Placenta	
	Model 1	N	651,746		854,999		1,524,996		22,352		29,375		49,915	
		N, %	5536	0.8%	4218	0.5%	7314	0.5%	655	2.9%	295	1.0%	509	1.0%
	Model 2	N	43,160		55,723		99,401		17,343		22,907		39,014	
		N, %	741	1.7%	1164	2.1%	799	0.8%	615	3.5%	323	1.4%	426	1.1%
			AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Diabetes	Model 1	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		Pregestational	*1.53*	*0.95, 2.48*	0.80	0.48, 1.33	*1.02*	*0.76, 1.37*	1.03	0.14, 7.51	–	–	0.38	0.05, 2.72
		Gestational	***1.28***	***1.04, 1.58***	*1.03*	*0.86, 1.24*	0.93	0.83, 1.05	*1.23*	*0.63, 2.37*	*1.43*	*0.82, 2.52*	0.79	0.53, 1.19
	Model 2	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		Pregestational	0.46	0.06, 3.27	1.01	0.44, 2.32	*1.69*	*0.83, 3.44*	–	–	0.85	0.12, 6.19	0.26	0.02, 4.25
		Gestational	1.01	0.60, 1.68	0.79	0.55, 1.13	***1.41***	***1.08, 1.84***	*1.26*	*0.65, 2.45*	*1.10*	*0.61, 1.99*	0.83	0.55, 1.25
Hypertension	Model 1	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		Pregestational	***1.37***	***1.12, 1.67***	0.49	0.36, 0.68	***1.77***	***1.52, 2.07***	*1.06*	*0.55, 2.02*	1.00	0.41, 2.44	*1.40*	*0.75, 2.61*
		Gestational	***1.52***	***1.34, 1.72***	0.54	0.44, 0.65	***1.96***	***1.79, 2.14***	*1.31*	*0.98, 1.74*	0.50	0.30, 0.83	0.82	0.59, 1.15
	Model 2	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		Pregestational	*1.39*	*0.88, 2.20*	0.61	0.37, 1.01	***1.79***	***1.21, 2.65***	*1.05*	*0.58, 1.89*	0.45	0.14, 1.41	0.83	0.37, 1.88
		Gestational	*1.02*	*0.73, 1.42*	0.55	0.40, 0.74	*1.16*	*0.87, 1.56*	*1.27*	*0.98, 1.66*	0.58	0.38, 0.87	0.77	0.54, 1.08
Fertility	Model 1	Fertile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Group		Subfertile	*1.49*	*0.77, 2.89*	*1.30*	*0.73, 2.32*	***1.52***	***1.11, 2.06***	*2.09*	*0.64, 6.81*	*1.14*	*0.22, 5.97*	*1.16*	*0.62, 2.17*
		IVF	***1.53***	***1.38, 1.70***	***3.79***	***3.48, 4.13***	***1.68***	***1.52, 1.85***	*1.16*	*0.97, 1.37*	***2.19***	***1.63, 2.94***	*1.23*	*0.99, 1.52*
	Model 2	A-fresh	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		A-thawed	***1.49***	***1.24, 1.80***	0.54	0.45, 0.65	0.63	0.51, 0.78	*1.26*	*0.99, 1.61*	0.66	0.44, 0.99	0.75	0.54, 1.04
		D-fresh	***1.52***	***1.16, 2.00***	0.74	0.59, 0.93	0.87	0.66, 1.14	***1.76***	***1.31, 2.34***	0.90	0.61, 1.32	0.93	0.66, 1.31
		D-thawed	0.83	0.52, 1.34	0.68	0.50, 0.94	0.73	0.49, 1.08	*1.58*	*0.98, 2.54*	1.15	0.63, 2.10	0.57	0.27, 1.19

Models adjusted for maternal age, parity, hypertension and diabetes (pregestational and gestational), placental complications (placenta previa, abruptio placenta, and excessive bleeding), mode of delivery, infant sex, length of gestation, small-for-gestation birthweight, State of residence, year of birth, and fertility status. For model 1, the study population was categorized by fertility status as fertile (reference), subfertile, and IVF (limited to autologous-fresh cycles only); for model 2, the study population was limited to IVF-conceived pregnancies as autologous-fresh (reference), autologous-thawed, donor-fresh, donor-thawed

Italicized AORs and 95% CIs are increased; those that are additionally emphasized in bold are significantly increased

Table 5 Risks of adverse outcomes, infant morbidity, and infant mortality by maternal fertility group: singletons

			Very early preterm		Early preterm		Preterm		SGA	
	Model #*		22–27 weeks		22–32 weeks		22–36 weeks		(≤ − 1.28)	
Infants	Model 1	N	2,308,528		2,308,528		2,308,528		2,303,434	
Outcome		N, %	11,543	0.5%	37,751	1.6%	191,214	8.3%	194,057	8.4%
	Model 2	N	143,644		143,644		143,644		143,341	
		N, %	1104	0.77%	3767	2.62%	17,446	12.15%	12,044	8.4%
			AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Fertility	Model 1	Fertile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Group		Subfertile	***2.12***	***1.74, 2.57***	***1.53***	***1.35, 1.74***	***1.41***	***1.33, 1.51***	1.01	0.94, 1.09
		IVF	***1.48***	***1.37, 1.61***	***1.52***	***1.45, 1.59***	***1.48***	***1.45, 1.51***	***1.13***	***1.10, 1.15***
IVF	Model 2	Autologous, fresh	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Group		Autologous, thawed	**1.14**	**0.97, 1.33**	0.93	0.85, 1.02	0.92	0.88, 0.96	0.58	0.54, 0.61
		Donor, fresh	**1.02**	**0.81, 1.29**	**1.17**	**1.04, 1.32**	**1.22**	**1.15, 1.30**	0.82	0.76, 0.89
		Donor, thawed	**1.58**	**1.19, 2.11**	**1.50**	**1.29, 1.76**	**1.45**	**1.33, 1.56**	0.76	0.69, 0.85
Co-morbidities	Model 1	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Hypertension		Pregestational	***3.12***	***2.83, 3.43***	***3.51***	***3.33, 3.71***	***2.81***	***2.73, 2.89***	***1.58***	***1.52, 1.64***
		Gestational	***2.07***	***1.93, 2.22***	***3.36***	***3.25, 3.48***	***3.23***	***3.18, 3.29***	***1.66***	***1.62, 1.70***
	Model 2	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		Pregestational	***2.04***	***1.67, 2.49***	***2.89***	***2.61, 3.19***	***3.17***	***3.00, 3.35***	***1.58***	***1.47, 1.71***
		Gestational	***2.14***	***1.55, 2.95***	***2.50***	***2.12, 2.95***	***2.35***	***2.14, 2.58***	***1.51***	***1.33, 1.71***
Co-morbidities	Model 1	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Diabetes		Pregestational	***1.43***	***1.19, 1.72***	***1.55***	***1.40, 1.70***	***2.34***	***2.23, 2.45***	0.74	0.68, 0.80
		Gestational	0.58	0.52, 0.65	0.93	0.88, 0.98	***1.29***	***1.27, 1.32***	0.83	0.81, 0.85
	Model 2	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		Pregestational	0.42	0.29, 0.61	***2.89***	***2.61, 3.19***	***3.17***	***3.00, 3.35***	0.98	0.90, 1.06
		Gestational	*1.24*	*0.63, 2.42*	***2.50***	***2.12, 2.95***	***2.35***	***2.14, 2.58***	0.79	0.60, 1.04
Length of	Model 1	Term (≥ 37 weeks)	–	–	–	–	–	–	1.00	Reference
Gestation		Preterm (< 37 weeks)	–	–	–	–	–	–	0.95	0.93, 0.97
		Early Preterm (< 32 weeks)	–	–	–	–	–	–	***1.22***	***1.17, 1.27***
		Very early preterm (< 28 weeks)	–	–	–	–	–	–	***1.36***	***1.28, 1.44***
	Model 2	Term (≥ 37 weeks)	–	–	–	–	–	–	1.00	Reference
		Preterm (<37 weeks)	–	–	–	–	–	–	0.99	0.93, 1.05
		Early Preterm (< 32 weeks)	–	–	–	–	–	–	***1.27***	***1.12, 1.44***
		Very early preterm (< 28 weeks)	–	–	–	–	–	–	***1.71***	***1.44, 2.04***
Placental	Model 1	None	1.00	Reference	1.00	Reference	1.00	Reference	–	–
Complications		Other excessive bleeding	***2.39***	***1.93, 2.96***	***1.95***	***1.70, 2.24***	***1.46***	***1.34, 1.58***	–	–
		Placenta previa	***2.43***	***1.96, 3.00***	***3.67***	***3.29, 4.10***	***6.94***	***6.52, 7.40***	–	–
		Abruptio placenta	***13.90***	***12.69, 15.22***	***13.72***	***12.93, 14.55***	***9.52***	***9.07, 9.98***	–	–
	Model 2	None	1.00	Reference	1.00	Reference	1.00	Reference	–	–
		Other excessive bleeding	***2.95***	***1.82, 4.79***	***2.23***	***1.64, 3.04***	***1.35***	***1.10, 1.65***	–	–

Table 5 (continued)

	Placenta previa	***1.64***	***1.02, 2.63***	***2.65***	***2.12, 3.31***	***6.54***	***5.79, 7.39***	–	–
	Abruptio placenta	***9.53***	***7.12, 12.77***	***9.77***	***8.17, 11.69***	***7.04***	***6.09, 8.14***	–	–

	LGA		NICU		Neonatal		Infant	
	(≥ 1.28)		Admission		Death		Death	
Infants	2,303,434		1,279,495		2,331,440		2,331,440	
Outcome	221,179	9.6%	78,387	6.1%	5583	0.24%	9338	0.40%
	143,341		79,622		145,622		145,622	
	14,625	10.2%	6628	8.3%	385	0.26%	536	0.37%
	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Fertility	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Group	0.93	0.87, 0.99	***1.19***	***1.09, 1.29***	***1.44***	***1.06, 1.96***	*1.16*	*0.88, 1.53*
	0.86	0.84, 0.88	***1.07***	***1.02, 1.12***	0.75	0.64, 0.86	0.73	0.65, 0.83
IVF	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Group	***1.58***	***1.52, 1.65***	***1.10***	***1.02, 1.19***	***1.36***	***1.03, 1.79***	***1.28***	***1.01, 1.63***
	1.18	***1.10, 1.26***	***1.14***	***1.03, 1.27***	1.01	0.65, 1.57	0.91	0.63, 1.32
	1.26	***1.15, 1.37***	*1.11*	*0.96, 1.28*	*1.23*	*0.72, 2.10*	*1.18*	*0.76, 1.84*
Co-morbidities	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Hypertension	0.90	0.87, 0.94	***1.52***	***1.44, 1.61***	0.60	0.50, 0.73	0.71	0.61, 0.83
	0.98	0.96, 1.01	***1.67***	***1.61, 1.72***	0.49	0.43, 0.56	0.60	0.54, 0.66
	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	0.90	0.83, 0.97	***1.53***	***1.37, 1.70***	0.45	0.28, 0.70	*1.18*	*0.32, 0.69*
	0.89	0.79, 1.01	***1.28***	***1.06, 1.55***	0.26	0.10, 0.67	0.58	0.32, 1.06
Co-morbidities	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Diabetes	***3.06***	***2.92, 3.19***	***2.87***	***2.68, 3.06***	1.17	0.88, 1.56	*1.28*	*1.02, 1.60*
	1.81	***1.78, 1.84***	***1.71***	***1.65, 1.76***	0.85	0.72, 0.99	0.86	0.77, 0.97
	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	1.36	***1.27, 1.46***	***1.59***	***1.44, 1.77***	0.62	0.32, 1.19	0.69	0.42, 1.14
	2.31	***1.92, 2.77***	***2.22***	***1.71, 2.89***	0.66	0.15, 2.96	0.42	0.09, 1.87
Length of	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Gestation	***1.49***	***1.46, 1.51***	***11.11***	***10.90, 11.32***	***7.24***	***6.61, 7.93***	***4.59***	***4.30, 4.91***
	1.37	***1.33, 1.43***	***68.39***	***65.75, 71.15***	***43.05***	***39.15, 47.33***	***22.21***	***20.63, 23.92***
	1.18	***1.12, 1.26***	***73.43***	***69.15, 77.97***	***496.87***	***462.44, 533.86***	***234.11***	***221.55, 247.37***
	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	1.01	0.95, 1.07	***11.79***	***11.05, 12.58***	***6.84***	***4.52, 10.36***	***5.54***	***4.02, 7.62***
	0.66	0.57, 0.76	***75.42***	***66.05, 86.13***	***56.81***	***39.01, 82.71***	***40.99***	***30.46, 55.10***

Table 5 (continued)

	0.67	0.53, 0.84	*77.40*	*62.67, 95.60*	*631.31*	*462.02, 862.64*	*407.65*	*318.99, 520.95*
Placental	–	–	–	–	–	–	–	–
Complications	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–

Models adjusted for maternal age, parity, hypertension and diabetes (pregestational and gestational), placental complications (placenta previa, abruptio placenta, and excessive bleeding), mode of delivery, infant sex, length of gestation, small-for-gestation birthweight, State of residence, year of birth, and fertility status. For model 1, the study population was categorized by fertility status as fertile (reference), subfertile, and IVF (limited to autologous-fresh cycles only); for model 2, the study population was limited to IVF-conceived pregnancies as autologous-fresh (reference), autologous-thawed, donor-fresh, donor-thawed. Italicized AORs and 95% CIs are increased; those that are additionally emphasized in bold are significantly increased

diseases related to short gestation and low birthweight (ICD-10 code P07). These two causes ranked 9 and 10 nationally (2.0% of deaths), ranked 10 and 9 among study singletons (3.6% of deaths), and ranked 4 and 3 among study twins (11.4% of deaths).

Discussion

This analysis of nationally-representative data provides a contemporary picture of infant morbidity and mortality by maternal fertility status in the USA (Figure 1). While prematurity was the major factor associated with infant morbidity and mortality, these analyses demonstrate the substantial role of placental complications, and the contribution of pregestational and gestational hypertension and diabetes to both adverse outcomes. These analyses demonstrate the significant risks associated with subfertile and IVF births, and in IVF pregnancies from cycles using donor oocytes and/or thawed embryos. In addition to being older and of lower parity, subfertile and IVF-treated women begin pregnancy with a higher incidence of chronic disease (hypertension and diabetes) compared to their fertile counterparts, and are more likely to develop gestational hypertension and diabetes, as well as placental complications. These findings confirm and expand our prior population-based studies in Massachusetts of greater risks of bleeding and placental complications among IVF-treated women [31, 32].

Both pregestational and gestational diabetes and hypertension, particularly the latter, were associated with greater risks of placental complications. In line with other rising trends, diabetes and hypertension, both pregestational and gestational, have increased among women of childbearing ages. In their analysis of the Nationwide Inpatient Sample from 1994 to 2004, Albrecht et al. [33] reported that over this decade period the rates for all types of diabetes increased, including > 50% increase for type 1 and gestational diabetes, and greater than fourfold increase for type 2. Older maternal age was an independent predictor of any diabetes among delivery hospitalizations. Hypertensive disorders in pregnancy are also rising in the US, with older maternal age and obesity being major contributing factors; these disorders are associated with substantial risks for adverse outcomes and severe morbidity [34–36]. An evaluation of the women ages 20–44 in the 1999–2008 NHANES reported a prevalence of hypertension to be 8% (with 4.2% on anti-hypertensive medication), with significant independent risk factors of older age, non-Hispanic black race, diabetes mellitus, chronic kidney disease, and higher BMI; obesity was associated with more than a fourfold increased risk of hypertension [34]. National studies have documented the increasing contribution of pre-existing

Table 6 Risks of adverse outcomes, infant morbidity, and infant mortality by maternal fertility group and plurality at birth: twins

			Very early preterm		Early preterm		Preterm		SGA	
	Model #*		22–27 weeks		22–32 weeks		22–36 weeks		(≤ − 1.28)	
Infants	Model 1	N	75,565		75,565		75,565		150,628	
Outcome		N, %	2760	3.7%	10,740	14.2%	44,090	58.3%	33,021	21.9%
	Model 2	N	58,110		58,110		58,110		115,847	
		N, %	1831	3.15%	8105	14.0%	34,530	59.4%	24,086	20.8%
			AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Fertility	Model 1	Fertile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Group		Subfertile	***1.77***	***1.44, 2.18***	***1.42***	***1.25, 1.61***	***1.14***	***1.04, 1.26***	0.93	0.86, 1.01
		IVF	0.88	0.81, 0.97	0.97	0.92, 1.02	***1.07***	***1.03, 1.11***	1.02	0.99, 1.05
IVF	Model 2	Autologous, fresh	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Group		Autologous, thawed	0.97	0.85, 1.12	1.01	0.94, 1.08	0.97	0.92, 1.02	0.60	0.57, 0.63
		Donor, fresh	0.89	0.74, 1.07	***1.15***	***1.05, 1.26***	***1.20***	***1.12, 1.28***	0.83	0.78, 0.87
		Donor, thawed	*1.12*	*0.83, 1.52*	***1.23***	***1.06, 1.42***	***1.35***	***1.21, 1.51***	0.77	0.70, 0.85
Co-morbidities	Model 1	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Hypertension		Pregestational	***1.29***	***1.00, 1.67***	***1.26***	***1.10, 1.46***	***2.29***	***2.02, 2.59***	***1.18***	***1.08, 1.30***
		Gestational	0.45	0.37, 0.54	0.88	0.82, 0.95	***2.29***	***2.15, 2.43***	***1.12***	***1.07, 1.17***
	Model 2	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		Pregestational	0.51	0.41, 0.62	1.01	0.94, 1.09	***2.62***	***2.46, 2.79***	***1.16***	***1.10, 1.22***
		Gestational	***1.40***	***1.05, 1.87***	***1.37***	***1.17, 1.59***	***2.53***	***2.21, 2.90***	***1.25***	***1.12, 1.38***
Co-morbidities	Model 1	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Diabetes		Pregestational	*1.12*	*0.67, 1.87*	***1.58***	***1.23, 2.03***	***1.43***	***1.14, 1.79***	0.96	0.80, 1.15
		Gestational	0.64	0.52, 0.79	1.04	0.95, 1.14	***1.08***	***1.01, 1.16***	0.92	0.87, 0.97
	Model 2	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
		Pregestational	0.70	0.56, 0.88	1.05	0.96, 1.16	***1.09***	***1.01, 1.17***	0.93	0.88, 0.99
		Gestational	1.06	0.53, 2.11	1.34	0.97, 1.84	*1.15*	*0.89, 1.50*	*1.08*	*0.88, 1.34*
Length of	Model 1	Term (≥37 weeks)	–	–	–	–	–	–	1.00	Reference
Gestation		Preterm (<37 weeks)	–	–	–	–	–	–	0.44	0.43, 0.46
		Early Preterm (<32 weeks)	–	–	–	–	–	–	0.22	0.21, 0.23
		Very early preterm (<28 weeks)	–	–	–	–	–	–	0.21	0.19, 0.23
	Model 2	Term (≥37 weeks)	–	–	–	–	–	–	1.00	Reference
		Preterm (<37 weeks)	–	–	–	–	–	–	0.44	0.42, 0.45
		Early Preterm (<32 weeks)	–	–	–	–	–	–	0.22	0.21, 0.24
		Very early preterm (<28 weeks)	–	–	–	–	–	–	0.19	0.17, 0.21
Placental	Model 1	None	1.00	Reference	1.00	Reference	1.00	Reference	–	–
Complications		Other excessive bleeding	*1.17*	*0.80, 1.70*	*1.20*	*0.97, 1.49*	*1.08*	*0.91, 1.28*	–	–
		Placenta previa	0.75	0.36, 1.55	***1.79***	***1.36, 2.37***	***3.48***	***2.56, 4.71***	–	–
		Abruptio placenta	***5.79***	***4.52, 7.41***	***5.13***	***4.28, 6.16***	***3.61***	***2.85, 4.57***	–	–
	Model 2	None	1.00	Reference	1.00	Reference	1.00	Reference	–	–
		Other excessive bleeding	0.71	0.43, 1.19	*1.02*	*0.81, 1.29*	0.95	0.79, 1.13	–	–

Table 6 (continued)

	Placenta previa		0.94	0.49, 1.81	***2.00***	***1.54, 2.60***	***3.63***	***2.69, 4.90***	–	–
	Abruptio placenta		***6.84***	***5.21, 8.99***	***5.23***	***4.28, 6.38***	***3.21***	***2.50, 4.13***	–	–
	LGA		NICU		Neonatal		Infant			
	(≥ 1.28)		Admission		Death		Death			
Infants	150,628		79,104		152,939		152,939			
Outcome	2585	1.7%	25,421	32.1%	1939	1.27%	2506	1.64%		
	115,847		61,505		117,837		117,837			
	2001	1.7%	20,371	33.1%	1122	0.95%	1451	1.23%		
	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI		
Fertility	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference		
Group	0.94	0.74, 1.19	***1.15***	***1.05, 1.26***	***1.40***	***1.08, 1.82***	*1.24*	*0.97, 1.57*		
	0.83	0.76, 0.91	***1.13***	***1.08, 1.19***	0.69	0.61, 0.78	0.67	0.61, 0.75		
IVF	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference		
Group	***1.70***	***1.51, 1.91***	0.96	0.90, 1.02	1.01	0.82, 1.24	0.97	0.81, 1.17		
	1.25	***1.06, 1.47***	***1.15***	***1.07, 1.24***	0.93	0.71, 1.21	0.97	0.77, 1.22		
	1.32	***1.02, 1.72***	1.09	0.96, 1.23	0.87	0.56, 1.35	0.78	0.52, 1.16		
Co-morbidities	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference		
Hypertension	0.93	0.70, 1.23	***1.39***	***1.20, 1.61***	0.78	0.53, 1.13	0.83	0.60, 1.16		
	1.05	*0.91, 1.20*	***1.48***	***1.39, 1.57***	0.56	0.43, 0.74	0.63	0.50, 0.79		
	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference		
	0.86	0.74, 1.00	***1.62***	***1.52, 1.72***	0.53	0.39, 0.73	0.64	0.50, 0.83		
	0.84	0.61, 1.14	***1.46***	***1.25, 1.71***	0.78	0.51, 1.19	0.83	0.57, 1.22		
Co-morbidities	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference		
Diabetes	***2.12***	***1.45, 3.11***	***1.58***	***1.28, 1.96***	0.78	0.37, 1.66	1.05	0.58, 1.92		
	1.39	***1.20, 1.61***	***1.22***	***1.14, 1.31***	0.89	0.68, 1.16	0.86	0.69, 1.09		
	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference		
	1.29	***1.09, 1.52***	***1.28***	***1.19, 1.37***	0.81	0.59, 1.10	0.80	0.61, 1.05		
	1.76	***1.06, 2.92***	***1.58***	***1.22, 2.05***	***2.22***	***1.03, 4.78***	***2.16***	***1.09, 4.28***		
Length of	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference		
Gestation	***1.89***	***1.70, 2.10***	***10.66***	***10.15, 11.19***	***2.64***	***1.98, 3.53***	***2.27***	***1.85, 2.79***		
	4.58	***4.07, 5.16***	***74.42***	***69.06, 80.20***	***17.85***	***13.45, 23.68***	***13.68***	***11.14, 16.81***		
	8.84	***7.71, 10.14***	***51.95***	***46.91, 57.53***	***499.48***	***386.61, 645.30***	***299.74***	***248.67, 361.30***		
	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference		
	1.86	***1.65, 2.09***	***10.81***	***10.23, 11.42***	***2.79***	***1.93, 4.05***	***2.39***	***1.80, 3.17***		
	3.96	***3.45, 4.53***	***73.27***	***67.36, 79.70***	***22.27***	***15.57, 31.85***	***17.80***	***13.51, 23.45***		

Table 6 (continued)

	8.64	*7.37, 10.14*	*65.40*	*57.42, 74.48*	*540.5*	*387.13, 754.63*	*380.01*	*293.77, 491.55*
Placental	–	–	–	–	–	–	–	–
Complications	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–

The N for the very early preterm, early preterm, and preterm outcomes is based on pregnancies, not infants. Models adjusted for maternal age, parity, hypertension and diabetes (pregestational and gestational), placental complications (placenta previa, abruptio placenta, and excessive bleeding), mode of delivery, infant sex, length of gestation, small-for-gestation birthweight, State of residence, year of birth, and fertility status. For model 1, the study population was categorized by fertility status as fertile (reference), subfertile, and IVF (limited to autologous-fresh cycles only); for model 2, the study population was limited to IVF-conceived pregnancies as autologous-fresh (reference), autologous-thawed, donor-fresh, donor-thawed. Italicized AORs and 95% CIs are increased; those that are additionally emphasized in bold are significantly increased

chronic disease to the rise in maternal morbidity and pregnancy-related mortality [37–40].

A consistent finding in IVF and ART pregnancies is an increased risk for uterine bleeding and placental complications, regardless of plurality [41–47]. IVF placentas have been documented to have altered morphology and gene expression, which may result in compromised development [48–51]. In their analysis of all births in Norway in 1999–2009, Ebbing et al. [46] reported increased risks for velamentous and marginal cord insertions with ART (twofold for singletons, and fourfold for twins), and a 20–80% risk of recurrence. Abnormal cord insertions were associated with a constellation of factors present in greater frequency among women who conceived after ART treatment (pre-existing medical conditions, older maternal age, pregnancy complications), as well as being associated with adverse pregnancy outcomes more common among the IVF and non-IVF ART populations (vaginal bleeding, placental complications, non-vertex presentation, prematurity, and birth defects). The authors suggest that these placental conditions share etiologic factors, and support the assumption that velamentous and marginal cord insertions represent a continuum of conditions that occur as a consequence of altered placental development. Other studies have shown that maternal pre-existing factors may lead to placental insufficiency and account for as much as one-third of spontaneous preterm births [52–54].

The use of frozen embryo transfer has increased by more than 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 [55–60]. 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 birthweights, pregnancy-induced hypertension, and placenta accreta [61–68].

Strengths and limitations

A major strength of this study is that the SART CORS data was collected prior to and separately from the vital statistics data, so we expect no differential misclassification of infant morbidity and mortality with respect to IVF. These findings are subject to several limitations. We were unable to adjust for underreported factors, including obesity, smoking and alcohol use, and inadequate or excessive gestational weight gain, which are each known to be associated with both prematurity and infant mortality. Although the models were adjusted for maternal age, there may be other important age-related factors

Table 7 Distribution of infant, neonatal, and postneonatal mortality by plurality: leading causes of infant death

		All US births*			Study singletons			Study twins		
	ICD-10 Codes	Rank	Number	% of total Deaths	Rank	Number	% of total Deaths	Rank	Number	% of total Deaths
Infant mortality (birth to 364 days)										
All causes		–	23,161	–	–	8657	–	–	2404	–
Congenital malformations, deformations, and chromosomal abnormalities	Q00-Q99	1	4816	20.8	1	2200	25.4	2	317	13.2
Disorders related to short gestation and low birthweight	P07	2	3927	17.0	2	884	10.2	1	459	19.1
Sudden infant death syndrome	R95	3	1500	6.5	3	679	7.8	8	68	2.8
Newborn affected by maternal complications of pregnancy	P01	4	1402	6.1	4	268	3.1	3	232	9.7
Accidents (unintentional injuries)	V01-X59	5	1219	5.3	5	421	4.9	9	30	1.2
Newborn affected by complications of placenta, cord, and membranes	P02	6	841	3.6	6	242	2.8	7	101	4.2
Bacterial sepsis of newborn	P36	7	583	2.5	7	246	2.8	6	121	5.0
Respiratory distress of newborn	P22	8	488	2.1	8	245	2.8	4	157	6.5
Diseases of the circulatory system	I00-I99	9	460	2.0	9	211	2.4	9	44	1.8
Neonatal hemorrhage	P50-P52, P54	10	398	1.7	10	199	2.3	5	119	5.0
Neonatal mortality (birth to 27 days)										
All causes		–	15,282	–	–	5202		–	1855	
Disorders related to short gestation and low birthweight	P07	1	3855	25.2	2	819	15.7	1	424	22.9
Congenital malformations, deformations, and chromosomal abnormalities	Q00-Q99	2	3394	22.2	1	1482	28.5	2	251	13.5
Newborn affected by maternal complications of pregnancy	P01	3	1389	9.1	3	256	4.9	3	227	12.2
Newborn affected by complications of placenta, cord, and membranes	P02	4	829	5.4	5	228	4.4	7	99	5.3
Bacterial sepsis of newborn	P36	5	555	3.6	6	212	4.1	6	105	5.7
Respiratory distress of newborn	P22	6	479	3.1	4	229	4.4	4	150	8.1
Neonatal hemorrhage	P50-P52, P54	7	391	2.6	7	187	3.6	5	110	5.9
Intrauterine hypoxia and birth asphyxia	P20-P21	8	331	2.2	8	134	2.6	10	19	1.0
Necrotizing enterocolitis of newborn	P77	9	303	2.0	9	118	2.3	8	54	2.9
Atelectasis	P28.0-P28.1	10	261	1.7	10	77	1.5	9	34	1.8
Postneonatal mortality (28–364 days)										
All causes		–	7879	–	–	3449	–	–	544	–
Congenital malformations, deformations, and chromosomal abnormalities	Q00-Q99	1	1422	18.0	1	718	20.8	1	65	11.9
Sudden infant death syndrome	R95	2	1380	17.5	2	605	17.5	2	62	11.4
Accidents (unintentional injuries)	V01-X59	3	1084	13.8	3	339	9.8	6	25	4.6
Diseases of the circulatory system	I00-I99	4	361	4.6	4	154	4.5	5	26	4.8
Assault (homicide)	X85-Y09	5	253	3.2	5	96	2.8	10	7	1.3
Diarrhea and gastroenteritis of infectious origin	A09	6	205	2.6	7	41	1.2	8	22	4.0
Septicemia	A40-A41	7	190	2.4	6	83	2.4	7	23	4.2
Influenza and pneumonia	J09-J18	8	164	2.1	8	70	2.0	9	14	2.6
Chronic respiratory disease originating in the perinatal period	P27	9	89	1.1	10	59	1.7	4	30	5.5
Disorders related to short gestation and low birthweight	P07	10	72	0.9	9	65	1.9	3	32	5.9

*2016 deaths, from Heron M. Deaths: Leading Causes for 2016. National Vital Statistics Reports, July 26, 2018, vol. 67, no. 6, pp. 1–77

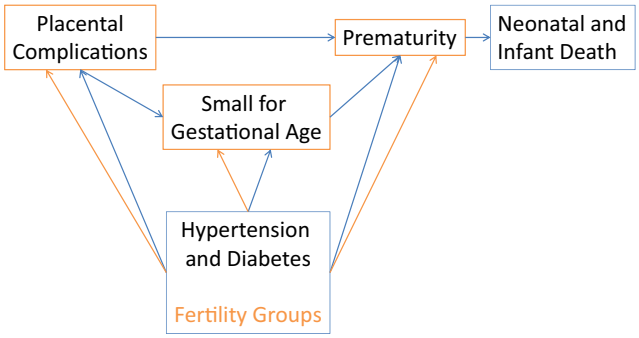

Fig. 1 A contemporary picture of infant morbidity and mortality by maternal fertility status in the USA

influencing outcomes that were not available, such as central obesity. In addition, we have previously shown that infertility treatment is underreported on the birth certificate, only accurately identifying about one-third of IVF-conceived infants [69]. The subfertile group is likely to also be underreported.

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Compliance with ethical standards

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

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