Mrs Maddison Evans
Committee Clerk
Standing Committee on Legislation
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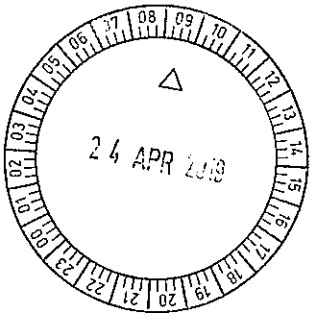

18 April 2019

Dear Mrs Evans

SUBMISSION TO THE LEGISLATION COMMITTEE INQUIRY – *Human Reproductive Technology and Surrogacy Legislation Amendment Bill 2018*

I would like to submit to the Legislation Committee inquiry the following peer reviewed articles:

Elenis, Evangelia, et al. "Adverse obstetric outcomes in pregnancies resulting from oocyte donation: a retrospective cohort case study in Sweden." *BMC pregnancy and childbirth*15.1 (2015): 247.

Luke, Barbara, et al. "Risk of severe maternal morbidity by maternal fertility status: a US study in 8 states." *American journal of obstetrics and gynecology* 220.2 (2019): 195-e1.

Masoudian, Pourya, et al. "Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis." *American journal of obstetrics and gynecology* 214.3 (2016): 328-339.

Nicolau, Yona, et al. "Outcomes of surrogate pregnancies in California and hospital economics of surrogate maternity and newborn care." *World Journal of Obstetrics and Gynecology*4.4 (2015): 102-107.

Woo, Irene, et al. "Perinatal outcomes after natural conception versus in vitro fertilization (IVF) in gestational surrogates: a model to evaluate IVF treatment versus maternal effects." *Fertility and sterility* 108.6 (2017): 993-998.

This research should be considered by the Committee as it evidences the harm surrogacy causes to gestational surrogates and the babies they carry. Extending surrogacy to single men and same sex male couples will increase the demand for egg donation and gestational surrogates in Western Australia, and will therefore increase the risk to women and children in this State.

Please find enclosed hard copies of these articles for consideration by the Committee.

Sincerely

[redacted]

Mrs Joan Smurthwaite

[redacted]

Elenis et al. BMC Pregnancy and Childbirth (2015) 15:247
DOI 10.1186/s12884-015-0687-9

BMC Pregnancy & Childbirth

RESEARCH ARTICLE Open Access

Adverse obstetric outcomes in pregnancies resulting from oocyte donation: a retrospective cohort case study in Sweden

Evangelia Elenis[1*], Agneta Skoog Svanberg[1], Claudia Lampic[2], Alkistis Skalkidou[1], Helena Åkerud[1] and Gunilla Sydsjö[3]

Abstract

Background: Oocyte donation has been associated to gestational diabetes, hypertensive disorders, placental abnormalities, preterm delivery and increased rate of caesarean delivery while simultaneously being characterized by high rates of primiparity, advanced maternal age and multiple gestation constituting the individual risk of mode of conception difficult to assess. This study aims to explore obstetrical outcomes among relatively young women with optimal health status conceiving singletons with donated versus autologous oocytes (via IVF and spontaneously).

Methods: National retrospective cohort case study involving 76 women conceiving with donated oocytes, 150 nulliparous women without infertility conceiving spontaneously and 63 women conceiving after non-donor IVF. Data on obstetric outcomes were retrieved from the National Birth Medical Register and the medical records of oocyte recipients from the treating University Hospitals of Sweden. Demographic and logistic regression analysis were performed to examine the association of mode of conception and obstetric outcomes.

Results: Women conceiving with donated oocytes (OD) had a higher risk of hypertensive disorders [adjusted Odds Ratio (aOR) 2.84, 95 % CI (1.04–7.81)], oligohydramnios [aOR 12.74, 95 % CI (1.24–130.49)], postpartum hemorrhage [aOR 7.11, 95 % CI (2.02–24.97)] and retained placenta [aOR 6.71, 95 % CI (1.58–28.40)] when compared to women who conceived spontaneously, after adjusting for relevant covariates. Similar trends, though not statistically significant, were noted when comparing OD pregnant women to women who had undergone non-donor IVF. Caesarean delivery [aOR 2.95, 95 % CI (1.52–5.71); aOR 5.20, 95 % CI (2.21–12.22)] and induction of labor [aOR 3.00, 95 % CI (1.39–6.44); aOR 2.80, 95 % CI (1.10–7.08)] occurred more frequently in the OD group, compared to the group conceiving spontaneously and through IVF respectively. No differences in gestational length were noted between the groups. With regard to the indication of OD treatment, higher intervention was observed in women with diminished ovarian reserve but the risk for hypertensive disorders did not differ after adjustment.

Conclusion: The selection process of recipients for medically indicated oocyte donation treatment in Sweden seems to be effective in excluding women with severe comorbidities. Nevertheless, oocyte recipients-despite being relatively young and of optimal health status- need careful counseling preconceptionally and closer monitoring prenatally for the development of hypertensive disorders.

Keywords: Hypertensive disorders, Indication for oocyte donation, Oocyte donation, Pregnancy complications

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Background

Oocyte donation (OD) is a well-established form of infertility treatment for women with premature ovarian failure, which may be caused by idiopathic or iatrogenic (after chemotherapy/ radiation/ surgery) diminished ovarian reserve, Turner syndrome, repeated unsuccessful IVF treatments and inheritable genetic maternal disorders [1]. In some countries, women with natural menopause can also receive treatment with donated oocytes.

Since the introduction of oocyte donation, there have been conflicting reports about the possible overrepresentation of this group among those presenting with complications during pregnancy and delivery. Several studies have suggested that an increase in the incidence of gestational diabetes [2], hypertensive disorders [3–8], placental abnormalities [9], preterm delivery [9] and increased rate of caesarean delivery [9] may be related to this treatment. According to research on immunological aspects of OD pregnancies, some clinical complications may theoretically arise, as the embryo resulting from oocyte donation is immunologically unrelated to the mother and this difference might predispose to placental pathology [10, 11]. On the other side, pregnancies following oocyte donation are often characterized by high rates of primiparity and multiple gestation [6, 12], factors that might introduce a bias when assessing the association between OD and pregnancy complications.

Sweden first permitted oocyte donation in 2003, solely on the basis of medical indication; oocyte donation now represents approximately 2.5 % of the total IVF and ICSI treatment cycles [13] with a total pregnancy and live birth rate per embryo transfer at about 30 %. Reproductive centers in Sweden, i.e. the University clinics that are allowed to perform IVF treatment with donated oocytes, practice mostly single embryo transfer (SET) and therefore the multiple pregnancy rate in IVF settings overall is now 4.8 % of all pregnancies [13]. It should be stressed that in 2010, only 10 % of oocyte donation cycles in Sweden were performed in women older than 40 years, which constitutes by far the lowest rate in Europe [14, 15].

To date, no previous studies have compared the association between oocyte donation and obstetric outcomes in a national setting. Thus the aim of this study was to investigate if singleton pregnancies following oocyte donation based on medical indication in a sample of Swedish women with optimal health status in fertile age are more often associated with adverse obstetric outcomes compared to (i) naturally conceived pregnancies (in nulliparous women without infertility) and (ii) pregnancies conceived after non donor IVF. Furthermore, we aimed to study whether outcomes differed depending on the specific indication leading to treatment.

Methods

Study sample and data collection

The present study is part of the *"Swedish multicenter study on gamete donation"*, a cohort study of donors and recipients of donated gametes receiving treatment at fertility clinics performing donation treatment in Sweden, at the University Hospitals in Stockholm, Gothenburg, Uppsala, Umeå, Linköping, Örebro and Malmö. Subfertile couples are accepted for inclusion on the gamete donation program after medical and psychological assessment performed at the treating clinics. During the period 2005–2008, consecutive couples starting donation treatment were approached regarding participation. The Index group comprises of women who later gave birth to one child following treatment with donated oocytes. Women who did not speak and/or read Swedish were excluded [16]. Written and oral information was given and participants signed an informed consent form allowing the research group to have access to the medical records.

Two control groups were used in order to assess the outcome;

a) Nulliparous women (Control group A) with spontaneously conceived pregnancies, singleton deliveries and no history of subfertility found in the medical register. All controls in group A were matched to the Index group in regard to age in three categories, ≤29, 30–34, ≥35 years, at a ratio of 2:1. With the exception of the eligibility criteria according to study design, Control group A was otherwise selected randomly. Unidentifiable information on the study subjects of Control group A was obtained and thus personal informed consent was not necessary for that group.
b) Heterosexual women (Control group B) undergoing in vitro fertilization (IVF) treatment with their own gametes due to couple infertility at the University hospitals mentioned above. All Swedish speaking women receiving traditional IVF treatment concurrently to the Index group were approached regarding participation on the *"Swedish multicentre study on gamete donation"* and constituted the original control cohort [16]. However solely those who conceived with singleton pregnancies during and on the imminent study period were finally included in Control group B. Age matching was not performed. The women were given written and oral information about the study and informed consent was obtained.

All medical data analyzed were retrieved from the Swedish Medical Birth Register (MBR), a Swedish population-based register started in 1973 and held by the Swedish National Board of Health and Welfare. MBR, which is a validated

register, includes information beginning with prenatal care and continuing through the delivery care and neonatal care [17–19]. Other medical information such as the treatment indication for the oocyte recipients originates from their treatment protocol after scrutinization of the medical record at each center.

The rationale for also including heterosexual women undergoing IVF as a control group was in order to investigate if the increased risks for oocyte recipients reported previously are attributable solely to donation. IVF pregnancies with autologous gametes are nowadays considered to be hampered by the underlying infertility, the characteristics of the infertile couple and/or the use of assisted reproductive techniques (i.e. conventional IVF or ICSI technique, fresh or frozen-thawed embryos) [20].

Our series include no maternal deaths. However one fetal intrauterine death in Control group A occurred on the 29th week of gestation.

Outcome measures

The medical data studied were based on the diagnosis according to the tenth version of the International Classification of Diseases (ICD-10) that the woman had received on the MBR. The following variables referring to medical practices and complications were studied: Mode of delivery [subdivided into Non Emergency and Emergency Caesarean Section, Normal Vaginal Delivery, Instrumental Delivery (with Vacuum extraction)], Induction of labor, Pregnancy Induced Hypertension, Preeclampsia, Eclampsia, HELLP syndrome or Hypertensive disorders of pregnancy as a whole (including all of the latter), Small for Gestational Age (SGA), Large for Gestational Age (LGA), Oligohydramnios, Polyhydramnios, Uterine Inertia, Fetal distress (either due to non reassuring heart beat on cardiotocography or acidemia/acidosis on fetal scalp blood test), Placenta praevia, Placental abruption, Retained Placenta with or without bleeding, Hemorrhage after labor, Nitrous Oxide gas or Epidural Anesthesia, Obstetrical lacerations of third or fourth grade, Total maternal hospital stay (from delivery date until hospital discharge). It should be noted that SGA and LGA were defined as a birth weight < −2SD or > +2 SD of the mean weight respectively as calculated by ultrasound scan compared to the expected value for the gestational length according to the Swedish growth standard [21]. Gestational age at delivery estimation was based on second-trimester ultrasound scan, or if this was not available then based on last menstrual period. For women who underwent in vitro fertilization and oocyte donation, gestational age was also calculated from the date of the embryo transfer. The ultrasound scan which is performed by specialized personnel during the 16th–19th gestational week constitutes common practice in Sweden and is attended by 98 % of pregnant women [22].

The medical indications that led to oocyte donation were also studied. Poor responders were classified according to the Bologna criteria [23] i.e. women with high FSH levels menstrual cycle day 3–5, women with cancelled IVF treatment due to suboptimal response as well as those with idiopathic premature ovarian insufficiency. The category "egg factor" is generally poorly defined but it is widely associated to oocyte-related infertility with sufficient quantity of oocytes but somehow defective quality.

Statistical analysis

All statistical analyses were performed using IBM SPSS v.20 (IBM Inc., Armonk, NY, USA). In all analyses, a p-value of <0.05 (two-sided) was considered statistically significant. Demographic and clinical characteristics were compared between Index women and Control group A and B respectively, using Student's t-test (normally distributed variables) and Mann-Whitney U test (non-normally distributed variables) for continuous data and Chi square test for categorical data. Afterwards the association between various obstetric outcomes and index/control group status was studied by first comparing oocyte recipients to spontaneously pregnant women (Control group A) and then oocyte recipients to women having conceived with conventional non-donor IVF (Control group B). The comparisons were performed with the use of Chi square or Fisher's exact test as well as logistic regression analyses; first a single regression model, i.e. without adjustment for socio-demographic or birth characteristics and afterwards by composing a multiple logistic regression model. A number of possible covariates based on results from previous studies were considered for inclusion in the multiple logistic regression model: maternal age as completed years on delivery day (two categories, <35 years or ≥35 years); body mass index (BMI, kg/m^2) defined as BMI recorded at first antenatal visit (two categories, <25 kg/m^2 or ≥ 25 kg/m^2); nicotine use as either smoking cigarettes or smokeless tobacco (*"snus"*) (no/yes) defined as smoker 3 months before conception or at first visit to the prenatal center in gestational week 10; gestational length (continuous variable); and presence of chronic medical conditions (no/yes). For the purpose of comparison, women who conceived spontaneously (Control group A) or by conventional IVF (Control group B) were referred to as having an odds ratio of 1.0. The odds ratios and corresponding 95 % confidence intervals were calculated.

Sensitivity analysis

According to the literature, nulliparous women have a higher risk for all adverse outcomes (i.e. nulliparity triples the risk for preeclampsia [24]). As our study group consisted of 92.1 % nulliparous (in contrast to 100 % in Control group A) we performed a sensitivity analysis in order to assess its possible influence. Parity did not

appear to influence the obstetric outcomes. Thus, we did not adjust for parity and we intentionally included multiparous women in the analysis, even though the risk for adverse perinatal outcomes is lower, in order not to compromise sample size, while minimizing any risks for false associations.

Details of ethics approval

The study was approved by the Regional Ethical Review Board in Linköping, Sweden (Nr M29–05, T113–07 and Nr 2012/289–32).

Results

Demographic data and obstetric characteristics concerning oocyte recipients (Index group), Control group A (spontaneous conception) and Control group B (non donor IVF) are summarized in Table 1. Although the median age differed between Index women and Control Group A, no significant differences were noted after stratification (initial matching according to study design). Regarding parity, all 150 women (100 %) in Control group A were nulliparous, in contrast to 58/63 women (92.1 %) in Control Group B and 70/76 women (92.1 %) of the Index group (5 multiparous with parity 2–3 and 6 multiparous with parity 2–4 respectively).

The chronic medical conditions reported were asthma, pre-gestational diabetes mellitus, hypothyroidism, epilepsy, mental health disorders, Crohn's disease, Systemic Lupus Erythematosus (SLE), Inflammatory Systemic Disease, Rheumatoid Arthritis (RA), renal disease (renal agenesis, renal insufficiency and renal transplantation), anemia, thrombosis and hematological diseases (data not shown). It should be noted that the prevalence of these conditions did not differ between the groups with the exception of hypothyroidism (7 oocyte recipients *vs* 1 in Control Group A and 0 in Control Group B), 40 % of which could be attributed to women with Turner syndrome, possibly due to careful pre-pregnancy screening of Turner women in Sweden [25]. University clinics are almost unanimous that women with severe comorbidities should be declined treatment; thus, only relatively healthy women were included in the Index group.

Tables 2 and 3 describe obstetric outcomes, either medical practices or complications, for the Index group and Control groups A and B. Women who underwent oocyte donation had overall more pregnancy complications compared to both Control groups (Tables 2 and 3). In particular, oligohydramnios was diagnosed more often among Index group versus Control group A (9.2 % *vs* 0.7 % respectively) [adjusted OR = 12.74, 95 % CI (1.24–130.49)]. The overrepresentation of oligohydramnios among the Index population might in part reflect an overdiagnosis due to frequent ultrasound scans on this group. Cesarean section was performed more often among women who conceived with donated oocytes (55.3 %) *vs* pregnant women with autologous oocytes (26 % in Control group A and 19 % in Control group B). It should be noted that when compared to Control

Table 1 Demographic and obstetrical data for oocyte recipients (Index group) and Control groups A and B

	Index group ($n = 76$)		Control group A ($n = 150$)		Control group B ($n = 63$)	
	Median (IQR)	Min-Max	Median (IQR)	Min-Max	Median (IQR)	Min-Max
Age, years	35.0 (4.0)	25–43	34.0 (4.0)***	19–36	33.0 (5.0)*	25–39
<35	36(47.4 %)		82(54.7 %)		42(66.7 %)*	
≥35	40(52.6 %)		68(45.3 %)		21(33.3 %)*	
	Median (IQR)	Min-Max	Median (IQR)	Min-Max	Median (IQR)	Min-Max
Estimated gestational age, week	40.0 (4.0)	28–42	40.0 (3.0)	28–43	39.0 (2.0)	36–42
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	Mean (SD)	Min-Max
BMI, kg/m^2	24.98(3.65)	18.0–34.6	24.32 (3.93)	18.1–41.0	24.06(3.54)	16.0–32.6
<25	33(47.1 %)		87(65.9 %)*		40(64.5 %)*	
≥25	37(52.9 %)		45(34.1 %)*		22(35.5 %)*	
Nulliparity	70/76(92.1 %)		150/150 (100 %)		58/63(92.1 %)	
Nicotine use						
No	63/68(92.6 %)		110/141(78 %)**		56/61(91.8 %)	
Yes	5 /68(7.4 %)		31/141 (22 %)**		5/61 (8.2 %)	
Chronic diseases						
No	55/76(72.4 %)		131/150(87.3 %)*		54/63(85.7 %)	
Yes	21/76(27.6 %)		19/150 (12.7 %)*		9/63 (14.3 %)	

*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

Table 2 Unadjusted and adjusted odds ratios (OR) and corresponding 95 % confidence intervals (CI) for delivery related outcomes for women treated with donated oocytes (Index group) compared to women with no history of infertility (Control group A)

Outcome	Index group n/N (%)	Control group A, n/N (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Normal delivery	21/76 (27.6 %)***	90/150 (60 %)	0.26 (0.14–0.50)*	0.30 (0.15–0.60)**
Instrumental delivery[a]	13/58 (22.4 %)	20/142 (14.1 %)	1.77 (0.74–4.25)	1.95 (0.75–5.09)
Caesarean Section (CS)	42/76 (55.3 %)***	39/150 (26 %)	3.69 (1.97–6.92)***	2.95 (1.52–5.71)**
Non emergency CS	18/76 (23.7 %)***	8/150 (5.3 %)	5.79 (2.36–14.22)***	5.13 (2.00–13.17)**
Emergency CS[a]	24/58(41.4 %)**	31/142(21.8 %)	2.49(1.20–5.13)**	1.93(0.88–4.22)
Induction of labor[a]	33/58 (56.9 %)***	31/142 (21.8 %)	3.34 (1.63–6.82)***	3.00 (1.39–6.44)**
Uterine Inertia, primary-secondary[a]	13/58 (22.4 %)	32/142 (22.5 %)	0.82 (0.36–1.84)	0.88 (0.36–2.16)
Hypertensive disorders of pregnancy[f]	12/76 (15.8 %)*	9/150 (6 %)	3.42 (1.32–8.86)*	2.84 (1.04–7.81)*
Pregnancy-Induced Hypertension	2/76 (2.6 %)	0/150	–	–
Preeclampsia	10/76 (13.2 %)	9/150 (6 %)	2.37 (0.92–6.12)	2.41 (0.84–6.89)
Fetal distress[a]	16/58 (27.6 %)*	21/142 (14.8 %)	2.62 (1.11–6.19)*	1.96 (0.78–4.97)
Very Preterm birth (<32 weeks)	3/76 (3.9 %)	3/150 (2.0 %)	6.19 (0.63–60.76)	6.48 (0.61–68.56)[b]
Preterm birth (<37 weeks)	13/76 (17.1 %)	13/150 (8.7 %)	2.42 (0.97–6.05)	1.86 (0.70–4.95)[b]
Maternal Hospitalization post partum				
≥2 days	73/75(97.3 %)**	127/148 (85.8 %)	10.40 (1.36–79.80)*	4.47 (0.53–37.76)[c]
≥3 days	59/75(78.7 %)**	86/148 (58.1 %)	2.64 (1.33–5.26)**	1.14 (0.51–2.58)[c]
Post-partum hemorrhage	12/76 (15.8 %)**	7/150 (4.7 %)	3.29 (1.12–9.70)**	7.11(2.02–24.97)[d]**
Retained placenta[e]	8/34 (23.5 %)**	4/111 (3.6 %)	7.58 (2.03–28.30)**	6.71 (1.58–28.40)*

All outcomes are adjusted for maternal age (<35, ≥35 years), BMI (<25 or ≥25 kg/m^2), Nicotine Use (Yes/No), Gestational length (continuous variable, weeks), Chronic diseases (Yes/No)

[a]Excluding all non-emergency Caesarean Section (CS)

[b]Not adjusted for gestational length but for all other covariates

[c]Adjusted for usual covariates, CS and Hypertensive disorders

[d]Adjusted for usual covariates and CS

[e]Excluding all CS

[f]Hypertensive disorders including preeclampsia, pregnancy induced hypertension, eclampsia or HELLP

*$p < 0.05$

**$p < 0.01$

***$p < 0.001$

group A, oocyte recipients had a higher risk for non emergency Cesarean section [aOR 5.13, 95 % CI(2.00–13.17)], whereas when compared to Control group B had higher risk for emergency Cesarean Section [aOR 15.98, 95 % CI (3.27–78.23)]. The prevalence of hypertensive disorders of pregnancy in women after oocyte donation (Index group) was 2.5-fold higher than in patients with spontaneous conception (Control group A) (15.8 % versus 6 %; $p = 0.017$). There were no differences in prevalence of eclampsia and pregnancy-induced hypertension. The preeclampsia rates were 13.2 % for oocyte recipients, whereas only 6 % for women having conceived spontaneously and 9.5 % for IVF women (Tables 2 and 3) which are comparable to that of the general obstetric population in Sweden (2–10 %) [26, 27]. It should be observed that when gestational hypertensive disorders were analysed independently and not as a unified group, statistical significance was not reached possibly due to the relatively small number of cases in each category. Nevertheless, no associations were found regarding complications such as pre-gestational and gestational diabetes mellitus, placenta praevia and placental abruption, SGA or LGA infant, polyhydramnios and obstetrical lacerations of 3rd or 4th grade (data not shown). Furthermore medical practices such as use of epidural analgesia or nitrous oxide use during active labor did not differ between groups.

In Table 4, the distribution of the medical indications that led to oocyte donation treatment among oocyte recipients is presented. The most common reason for receiving donated oocytes was premature ovarian failure or being "poor responder" [23] (48.7 %) followed by Turner syndrome (13.2 %) and bilateral oophorectomy or post chemotherapy (11.8 %).

In Table 5, a subgroup analysis within the Index group based on the indication of treatment and compared to Control group A is presented. The analysis revealed that induction of labor and caesarean section occurred more frequently among the group of women with premature ovarian insufficiency or who were "poor responders" (45.9 and 56.8 % respectively) compared to other indications of OD treatment (41.2 and 50 % respectively) or spontaneously conceived pregnancies (Table 5). Risk for

Table 3 Unadjusted and adjusted Odds Ratios (OR) and corresponding 95 % confidence intervals (CI) for delivery related outcomes for women treated with donated oocytes (Index group) compared to women treated with traditional IVF (Control group B)

Outcome	Index group n/N(%)	Control group B, n/N(%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Normal delivery	21/76(27.6 %)***	39/63(61.9 %)	0.25 (0.12–0.53)***	0.29 (0.13–0.65)**
Instrumental delivery[a]	13/58 (22.4 %)	12/53(22.6 %)	0.90(0.35–2.33)	0.86 (0.29–2.55)
Caesarean Section (CS)	42/76(55.3 %)***	12/63 (19 %)	6.01 (2.65–13.59)***	5.20 (2.21–12.22)***
Non emergency CS	18/76 (23.7 %)	10/63(15.9 %)	2.21 (0.91–5.40)	1.82 (0.71–4.66)
Emergency CS[a]	24/58(41.4 %)***	2/53 (3.8 %)	16.96 (3.68–78.24)***	15.98 (3.27–78.23)**
Induction of labor[a]	33/58(56.9 %)***	12/53(22.6 %)	3.19 (1.35–7.56)***	2.80 (1.10–7.08)*
Uterine Inertia, primary-secondary[a]	13/58 (22.4 %)*	4/53 (7.5 %)	3.24 (0.94–11.17)	3.67 (0.92–14.66)
Hypertensive disorders of pregnancy[f]	12/76 (15.8 %)	6/63 (9.5 %)	2.08 (0.73–5.93)	1.66 (0.54–5.08)
Pregnancy-Induced Hypertension	2/76 (2.6 %)	0	–	–
Preeclampsia	10/76 (13.2 %)	6/63 (9.5 %)	1.44 (0.49–4.21)	1.39 (0.44–4.42)
Fetal distress[a]	16/58 (27.6 %)*	5/53 (9.4 %)	3.22 (1.04–9.99)*	2.86 (0.83–9.86)
Very preterm birth (<32 weeks)	3/76 (3.9 %)	0	–	–
Preterm birth (<37 weeks)	13/76 (17.1 %)*	3/63 (4.8 %)	3.94 (1.04–14.88)*	3.45 (0.88–13.62)[b]
Maternal Hospitalization post partum				
≥2 days	73/75 (97.3 %)*	54/63(85.7 %)	10.87 (1.34–90.91)*	5.26 (0.55–50.35)[c]
≥3 days	59/75(78.7 %)**	35/63(55.6 %)	3.03 (1.39–6.58)**	1.74 (0.70–4.34)[c]
Post-partum hemorrhage	12/76 (15.8 %)	6/63 (6.5 %)	1.47 (0.49–4.42)	3.67(1.03–13.03) [d]*
Retained placenta[e]	8/34 (23.5 %)	4/51 (7.8 %)	3.83 (1.01–14.53)*	2.98 (0.73–12.18)

All outcomes are adjusted for maternal age (<35, ≥35 years), BMI (<25 or ≥25 kg/m^2), Nicotine Use (Yes/No), Gestational length (continuous variable, weeks), Chronic diseases (Yes/No)
[a]Exclude all non-emergency Caesarean Section (CS)
[b]Non adjusted for gestational length but for all other covariates
[c]Adjusted for usual covariates, CS and Hypertensive disorders
[d]Adjusted for usual covariates and CS
[e]Exclude all CS
[f]Hypertensive disorders including preeclampsia, pregnancy induced hypertension,eclampsia or HELLP
*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

postpartum hemorrhaging was highest for the subgroup "other indication" of OD treatment.

Discussion

Our analysis provides evidence that oocyte donation is associated with hypertensive disorders of pregnancy, oligohydramnios, induction of labor, delivery by caesarean section, retained placenta, post-partum hemorrhage and longer hospital stay after delivery even though oocyte recipients in our study are quite healthy and relatively young. The association between oocyte donation and hypertensive disorders of pregnancy remained significant even after adjustment for various covariates.

Table 4 Indication to infertility treatment among participating women in the oocyte donation group

Indication to oocyte donation	n	Percent (%)
Poor responder & Premature Ovarian Insufficiency (POI)	37	48.7
Turner syndrome	10	13.2
After oophorectomy/chemotherapy	9	11.8
"Egg factor"	6	7.9
Multiple unsuccessful IVF cycles	5	6.6
Genetic reasons	5	6.6
Unclassified	4	5.3
Total	76	100.0

The category "egg factor refers to oocyte-related infertility with sufficient quantity of oocytes that were somehow defective in quality

Although several previous studies investigating obstetric and perinatal pregnancy outcomes after oocyte donation have been performed, most of them lacked an appropriate control group; thus the only studies with a design similar to ours are the ones by Malchau et al. and Stoop et al. Malchau et al. [8] investigated perinatal outcomes in 375 pregnancies after oocyte donation in a Danish national cohort study and showed two- to threefold increased risk regarding hypertensive disorders and caesarean section in OD pregnancies when compared to IVF/ICSI and spontaneously conceived singleton pregnancies. It should however be noted that our study population, despite being of similar ethnical origin, comprises women younger than the women in the Danish cohort [8], thus strengthening the reported results. Stoop et al. [7], performed a matched-pair analysis with

Table 5 Unadjusted and adjusted Odds Ratios (OR) and corresponding 95 % confidence intervals (CI) for delivery related complications for women treated with donated oocytes compared to women who conceived spontaneously (Control group A), reported by cause for oocyte donation

	Oocyte recipients other[a]		Oocyte recipients POI[b]	
	Crude OR (95 % CI)	Adjusted OR (95 % CI)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Hypertensive disorders	4.13(1.30–13.05)*	3.13 (0.94–10.48)	3.49(1.12–10.92)*	3.42 (0.99–11.87)
Induction of labour[c]	2.53 (0.93–6.93)**	2.59 (0.88–7.65)	4.11(1.66–10.22)**	3.33 (1.25–8.82)*
Cesarean section	2.79 (1.21–6.46)*	2.35 (0.98–5.62)	4.08 (1.82–9.15)**	3.03 (1.28–7.15)*
Post-partum hemorrhage	3.42 (0.90–13.03)	7.04 (1.45–34.16)*[d]	2.93 (0.78–11.07)	5.97(1.11–32.15)*[d]
Uterine inertia[c]	0.36 (0.08–1.64)	0.42 (0.09–2.07)	1.01 (0.37–2.78)	0.93 (0.30–2.84)

[a]Women with Turner syndrome, oophorectomy/chemotherapy, "egg factor", multiple unsuccessful IVF cycles, genetic reasons, unclassified
[b]POI: Premature ovarian insufficiency and poor responders
All outcomes are adjusted for maternal age (<35, ≥35 years), BMI (<25 or ≥25 kg/m^2), Nicotine Use (No/Yes), Gestational length (continuous variable, weeks), Chronic diseases (No/Yes)
[c]Exclude all non-emergency CS
[d]Model adjusted for CS also
*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

regard to age, ethnicity, parity and plurality between OD and IVF conceived women with autologous oocytes. They reported a similar trend towards a higher incidence of pregnancy-induced hypertension, preterm birth, caesarean section and instrumental delivery in the OD study group [7]. In contrast to some previous reports, we did not demonstrate any increased risk for gestational diabetes among women having conceived through oocyte donation, possibly due to the lower age and even perhaps lower weight of our population [28–30].

Caesarean section was performed more often among oocyte recipients than controls in a national setting where vaginal delivery (84 % of all singleton deliveries in Sweden) is the mode of delivery of first choice [31]. It should, however, be noted that the high proportion of cesarean section cannot be solely attributed to the obstetrician's or woman's choice since elective (humanitarian) caesarean section did not differ between the groups (data not shown). Furthermore, the period during which they stayed at the hospital after delivery (≥3 days) was longer in the study group but the risk was eliminated after adjusting for the presence of hypertensive disorders, caesarean section and the usual covariates. Trends were also noted regarding preterm birth and very preterm birth but the overall gestational length did not differ between the groups. High risk for post partum hemorrhage was observed even after adjusting for operative delivery with greater prevalence than expected by previous reports [25, 32].

Finally, after investigating adverse obstetric outcomes with regard to the indication of OD treatment, a tendency towards greater maternal complications was observed for women with declining ovarian reserve. This is partly in accordance with the findings of Keegan et al. [33] and Pados et al. [34] who demonstrated that young oocyte recipients exhibited the highest rates of gestational hypertension and preeclampsia, which indicates a possible relationship between diminished ovarian function and hypertensive disorders. However, caution is advised in the interpretation of the data due to the limited size of the study population, as seen by the wide confidence interval.

Strengths and limitations of the study

The major strength of our study is its national design comprising all centers allowed to perform IVF treatment with donated oocytes in Sweden and hence recruiting a wide range of women from both urban and rural areas. Furthermore it is one of the few that compares three modes of conception [6, 8] and constitutes one of the largest series on singletons pregnancies after oocyte donation published thus far, with a well defined and age matched control group [7, 8] where the medical indication of the oocyte donation treatment for every woman was taken into account. In addition, in Sweden, antenatal care is standardized and free of charge with good availability of the public health system independently of social or employment status and educational level of the pregnant woman. Thus, the differences noted on the various outcomes cannot be vastly attributed to different level of obstetric care given. Finally, our study group comprises relatively young recipient women with ascertained health status with donated oocytes derived from young (≤35 years) fertile women and not through egg sharing from other infertile women undergoing ART. It should be stressed that the participating clinics at the nationwide oocyte donation program, despite not having a standardized way of making the evaluation of the recipients but rather following their own clinical policy, seem nevertheless to be unanimous

regarding the importance of relatively young age and good health status of the oocyte recipients.

One of the limitations of our study is the lack of power, as shown by the wide confidence intervals, which may limit the interpretation of some results. Moreover, due to the retrospective design of our study and because infertility is often unreported in obstetric records, we cannot exclude the possibility that there might be women with a history of infertility in Control group A. On the other hand, this fact would only lead to underestimation of associations. Finally in the assessment of the various outcomes, we did not take into account parameters such as donor age, paternal age, ART method (conventional IVF or ICSI) as well as if the pregnancy resulted from a cryopreserved or fresh embryo. It should however be noted that large series did not find donor age to have a significant association with perinatal outcome [7, 35]; this according to the authors might in part reflect the homogeneity of the oocyte donor population i.e. more than 98 % of donors reported being younger than 35 years. Similar conditions apply even in Sweden where according to common practice in the various IVF university clinics the vast majority of donors are anonymous, younger than 35 years and with proven fertility. In particular, the nationwide study on oocyte donation in Sweden reported a mean age of 31.5 ± 4.6 years for oocyte donors supporting the conclusions deducted [36].

Conclusion

Our study confirms that the evaluation process of oocyte recipients in Sweden appears to be successful in excluding women with severe comorbidities. However, oocyte recipients based on medical indication, despite being of young age and optimal health, have higher risks for adverse obstetric outcomes compared to women conceiving with autologous oocytes, regardless of mode of conception. Obstetricians should therefore provide careful counseling preconceptionally and closer monitoring prenatally regarding the development of hypertensive disorders.

Abbreviations

ART: Assisted reproductive technology; CS: Caesarean section; IVF: In vitro fertilization; LGA: Large for Gestational Age; MBR: Medical Birth Register; OD: Oocyte Donation; SGA: Small for Gestational Age.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

EE participated in the design of the study, performed the statistical analysis and prepared the manuscript. CL assisted in data collection and drafted the manuscript. GS and ASS conceived of the study, supervised the analysis and writing of the manuscript. HÅ and AS assisted substantially in the statistical analysis and drafted the manuscript. All authors read and approved the final version of the manuscript.

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OBSTETRICS

Risk of severe maternal morbidity by maternal fertility status: a US study in 8 states

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BACKGROUND: Over the past 2 decades the characteristics of women giving birth in the United States and the nature of the births themselves have changed dramatically, with increases in older maternal age, plural births, cesarean deliveries, and conception from infertility treatment.

OBJECTIVE: We sought to evaluate the risk of severe maternal morbidity by maternal fertility status, and for in vitro fertilization pregnancies, by oocyte source and embryo state combinations.

STUDY DESIGN: Women in 8 states who underwent in vitro fertilization cycles resulting in a live birth during 2004 through 2013 were linked to their infant's birth certificates; a 10:1 sample of births from non-in vitro fertilization deliveries were selected for comparison; those with an indication of infertility treatment on the birth certificate were categorized as subfertile, all others were categorized as fertile. In vitro fertilization pregnancies were additionally categorized by oocyte source (autologous vs donor) and embryo state (fresh vs thawed). Maternal morbidity was identified from the birth certificate, modeled using logistic regression, and reported as adjusted odds ratios [95% confidence intervals]. The reference group was fertile women.

RESULTS: The study population included 1,477,522 pregnancies (1,346,118 fertile, 11,298 subfertile, 80,254 in vitro fertilization autologous-fresh, 21,964 in vitro fertilization autologous-thawed, 13,218 in vitro fertilization donor-fresh, and 4670 in vitro fertilization donor-thawed pregnancies): 1,420,529 singleton, 54,573 twin, and 2420 triplet+ pregnancies. Compared to fertile women, subfertile and the 4 groups of in vitro fertilization—treated women had increased risks for blood transfusion and third- or fourth-degree perineal laceration (subfertile, 1.58 [1.23—2.02] and 2.08 [1.79—2.43]; autologous-fresh, 1.33 [1.14—1.54] and 1.37 [1.26—1.49]; autologous-thawed, 1.94 [1.60—2.36] and 2.10 [1.84—2.40]; donor-fresh, 2.16 [1.69—2.75] and 2.11 [1.66—2.69]; and donor-thawed, 2.01 [1.38—2.92] and 1.28 [0.79—2.08]). Also compared to fertile women, the risk of unplanned hysterectomy was increased for in vitro fertilization—treated women in the autologous-thawed group (2.80 [1.96—4.00]), donor-fresh group (2.14 [1.33—3.44]), and the donor-thawed group (2.46 [1.33—4.54]). The risk of ruptured uterus was increased for in vitro fertilization—treated women in the autologous-fresh group (1.62 [1.14—2.29]). Among women with a prior birth, the risk of blood transfusion after a vaginal birth was increased for subfertile women (2.91 [1.38—6.15]), and women in all 4 in vitro fertilization groups (autologous-fresh, 1.93 [1.23—3.01]; autologous-thawed, 2.99 [1.78—5.02]; donor-fresh, 5.13 [2.39—11.02]; and donor-thawed, 5.20 [1.83—14.82]); the risk after a cesarean delivery was increased in the autologous-thawed group (1.74 [1.29—2.33]) and the donor-fresh group (1.62 [1.07—2.45]). Unplanned hysterectomy was increased in the autologous-thawed (2.31 [1.43—3.71]) and donor-thawed (2.45 [1.06—5.67]) groups.

CONCLUSION: The risks of severe maternal morbidity are increased for subfertile and in vitro fertilization births, particularly in pregnancies that are not from autologous, fresh cycles.

Key words: autologous-fresh, autologous-thawed, blood transfusion, cesarean delivery, donor-fresh, donor-thawed, embryo state, in vitro fertilization, infertility, oocyte source, perineal laceration, peripartum hysterectomy, severe maternal morbidity, subfertility, twin and triplet births, unplanned hysterectomy

Introduction

Births in the United States from in vitro fertilization (IVF) have doubled from 2000 through 2015, and currently account for 1.8% of all births.[1–4] Although the use of autologous oocytes and fresh embryos has been the norm since IVF treatment began in the 1980s, in recent years there has been a national and international shift in practice to freeze-only, believed to provide better endometrial development than the controlled ovarian stimulation required with autologous-fresh transfers.[5–9] While there is growing evidence from clinical studies that the freeze-only approach is associated with better rates of implantation, clinical pregnancy, ongoing pregnancy, and live birth with thawed vs fresh embryo transfers,[10–12] little is known regarding the consequences at delivery.

Although an estimated 12% of reproductive-aged women and 9.4% of reproductive-aged men have ever used infertility services, IVF represents only a small portion of all infertility treatment used in the United States. Results of the 2006 through 2010 National Survey of Family Growth reported that the most commonly used infertility services among women ages 25—44 years included medical advice (9.4%), infertility testing (male or female, 7.3%), medical help to prevent miscarriage (6.8%), and ovulation drugs (5.8%). Artificial insemination was reported by 1.7% of women ages 25—44 years (~714,000 women), and surgery for blocked tubes by 1.3% of women (~531,000). Assisted reproductive technology (ART), including IVF, was the least common service ever used, reported by 0.7% of women ages 25—44 years (~275,000 women).[13] Among women with current infertility problems, an estimated 3.1% had ever used ART. The purpose of this analysis is to

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AJOG at a Glance

Why was this study conducted?
To evaluate the risks of severe maternal morbidity by maternal fertility status and plurality.

Key findings
Among the total study population, the risk of blood transfusion was increased for the subfertile group and the 4 in vitro fertilization groups; the risk of unplanned hysterectomy was increased for autologous-thawed, donor-fresh, and donor-thawed groups. Risk of ruptured uterus was increased for the autologous-fresh group.

What does this add to what is known?
The risks of severe maternal morbidity are increased for subfertile and in vitro fertilization–treated women, particularly in pregnancies that are not from autologous, fresh cycles.

evaluate the risk of severe maternal morbidity 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 (SART) Clinic Outcome Reporting System (CORS), to birth certificates as part of a larger study in 14 states on ART and risk of childhood cancer (National Institutes of Health grant R01 CA151973). The data for this analysis were limited to live births (≥22 weeks' gestation and ≥300 g birthweight) to mothers at least 18 years of age in study states in which the 2003 revision of the birth certificate had been implemented and its data available (California, Colorado, Florida, Michigan, New York, Ohio, Pennsylvania, and Texas).

SART CORS data

The SART maintains Health Insurance Portability and Accountability Act of 1996–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 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 <2%, with diagnosis fields ranging from 2–5%.[14]

Birth certificate data

The 2003 revision of the birth certificate includes specific severe maternal morbidities occurring within 24 hours before or after delivery: maternal transfusion; third- or fourth-degree perineal laceration (vaginal births); ruptured uterus; unplanned hysterectomy; and admission to intensive care. Also in the 2003 revision of the birth certificate, 3 check boxes were added to indicate: (1) the pregnancy resulted from infertility treatment ("if yes, check all that apply"); (2) fertility-enhancing drugs, artificial insemination, or intrauterine insemination; and (3) ART (eg, IVF, gamete intrafallopian transfer). Pregnancies that linked to the SART CORS cycles were categorized as IVF; pregnancies with an indication that they resulted from infertility treatment (via the infertility check box) but did not link to an IVF cycle were categorized as subfertile; the remaining pregnancies were categorized as fertile.

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 (New York, NY), the organization that maintains the CORS on behalf of SART, containing only the following factors: study-specific patient identification (ID) and cycle ID; woman's first name, 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; and 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 1 infant from a twin or triplet+ pregnancy. The files of the study children were then linked to each state's vital records. Once all data were linked and complete, the files were stripped of all identifying elements (eg, 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 deidentified files were then transmitted to the investigators using secure file transfer methods. For the investigators, Redshift Technologies Inc created a deidentified data file with the study-specific patient ID and cycle ID, and the IVF treatment parameters, and sent the file by secure transfer methods. We then merged the 2 deidentified 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.

TABLE 1
Maternal characteristics by fertility group and plurality

	Singletons						Twins						Triplets+[a]					
			IVF						IVF						IVF			
	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed
N, pregnancies	1,326,650	9142	56,037	16,997	8129	3574	19,116	1951	22,858	4686	4921	1041	352	205	1359	281	168	55
Maternal age, y																		
Mean (SD)	28.7 (5.9)	33.7 (5.2)	35.0 (4.3)	35.0 (4.3)	42.1 (4.7)	42.9 (5.1)	29.7 (5.8)	34.5 (5.4)	33.9 (4.0)	34.2 (4.1)	41.8 (4.8)	42.4 (5.2)	31.2 (5.6)	32.9 (5.2)	33.8 (3.9)	33.8 (4.2)	40.8 (4.7)	42.9 (5.2)
%																		
18–29	55.3	21.0	10.5	9.9	1.3	1.7	48.1	16.4	14.5	12.0	1.7	2.1	36.8	24.8	15.0	17.5	1.2	0.0
30–34	26.9	36.0	34.0	35.1	6.2	5.8	30.1	37.5	40.7	41.6	7.0	6.9	36.7	43.4	39.4	39.4	8.0	5.5
35–37	10.3	19.6	24.9	26.4	7.5	7.1	12.5	21.2	25.0	25.0	8.9	8.2	14.2	13.8	26.5	24.0	14.3	12.7
38–40	5.3	13.8	20.1	18.7	15.4	12.3	6.6	12.6	15.3	15.0	15.8	14.0	8.1	10.0	15.3	13.7	19.4	10.9
≥41	2.1	9.5	10.5	9.9	69.6	73.2	2.7	12.3	4.4	6.4	66.7	68.9	4.2	8.0	3.8	5.5	57.1	70.9
Hispanic ethnicity, %	26.4	7.3	8.6	9.4	8.0	9.4	20.7	6.8	11.1	13.3	8.2	6.7	18.8	9.9	4.8	5.3	4.5	5.2
Race, %																		
White	76.7	86.7	81.7	78.3	83.7	83.7	75.2	85.7	83.9	78.3	83.9	84.3	79.0	91.4	86.3	77.8	84.8	84.6
Black	13.2	4.0	4.8	5.3	4.5	5.2	17.4	4.1	4.4	6.1	5.3	4.9	15.0	3.3	5.3	9.2	6.6	11.5
Asian	9.5	8.9	13.2	16.1	11.5	10.9	7.0	10.0	11.5	15.4	10.5	10.6	5.2	4.6	8.4	12.6	7.9	3.8
Other	0.5	0.3	0.2	0.3	0.2	0.3	0.4	0.2	0.2	0.2	0.3	0.2	0.7	0.7	0.0	0.4	0.6	0.0
Education, %																		
<8th Grade	4.7	0.3	0.3	0.6	0.4	0.3	3.6	0.3	0.3	0.3	0.4	1.2	1.8	0.0	0.2	2.6	1.2	0.0
Some high school	12.1	1.5	1.0	1.2	0.9	0.8	10.3	1.3	1.0	1.0	0.8	0.8	6.7	1.6	1.4	2.1	0.0	0.0
High school graduate or GED	24.4	8.3	7.1	7.7	6.8	6.1	23.1	8.1	7.7	7.6	7.1	6.4	21.1	11.0	12.1	9.9	10.7	12.3
Some college or associate degree	27.0	20.9	18.5	18.1	16.3	18.6	27.2	17.8	19.6	19.2	17.2	20.5	27.2	28.1	23.1	26.6	24.1	20.4
Bachelor's degree	20.3	37.5	39.8	38.8	39.6	38.7	22.1	37.0	40.4	38.7	39.5	37.0	25.6	29.8	35.3	35.2	36.7	52.5
Postgraduate	11.6	31.6	33.3	33.6	36.1	35.4	13.6	35.5	31.0	33.1	34.9	34.1	17.6	29.5	27.9	23.7	27.2	14.8

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(continued)

TABLE 1
Maternal characteristics by fertility group and plurality *(continued)*

	Singletons					Twins					Triplets+[a]				
		IVF					IVF					IVF			
	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed
Parity, %																		
Nulliparous	38.7	56.4	70.0	51.9	69.9	50.9	20.2	29.7	40.4	32.2	39.3	29.7	16.1	16.9	26.8	21.6	25.3	17.4
1	33.0	29.9	22.4	34.1	21.7	35.7	35.4	42.0	43.6	42.5	43.1	41.0	26.0	28.0	29.4	27.8	29.6	25.9
≥2	28.2	13.6	7.6	14.0	8.4	13.4	44.5	28.3	16.0	25.3	17.6	29.2	57.9	55.1	43.8	50.6	45.1	56.7

Missing: age 0.012%, race 5.8%, parity 20%, education 1.5%; length of gestation 0.9%.

Means are weighted; SDs are not weighted.

GED, General Educational Development; *IVF*, in vitro fertilization.

[a] Includes triplets, quadruplets, quintuplets, and sextuplets.

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Although the family structure (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; ie, if the birth was recorded as a twin, each record would receive the weight of one-half and if a triplet, a weight of one-third. Summing the records in the same family using this weight would then estimate the mother's outcome correctly. (If it was possible to use frequencies instead of weights, both means and SD would be correctly estimated, but software [SAS; SAS Institute Inc, Cary, NC] does not allow frequencies <1.) Weighting reduces the estimate of the SD; therefore, the SD were computed without weights. The means and SD can be interpreted in the usual manner as estimates that apply to an observation.

Comparison groups

Women were classified as IVF-treated only if the state matched the subject to a record in the SART CORS; >90% of the women in SART CORS were identified by the matching. The IVF-treated subjects were then divided into 4 subgroups depending on the source of the oocyte (autologous or donor) and the state of the embryo (fresh or thawed). The control subjects were divided into 2 groups: fertile and subfertile; a woman was assigned to the subfertile group if she responded positively to any of the infertility questions on the birth certificate. Therefore, 6 maternal fertility status groups were created; the fertile women were treated as the reference group in the modeling.

Variables

Independent variables included maternal age at delivery (continuous and as 18–29, 30–34, 35–37, 38–40, 41–44, and ≥45 years), race (white, black, Asian, other) and Hispanic ethnicity, education (<8th grade, some high school, high school graduate or General Educational Development, some college or associate degree, bachelor degree, or postgraduate education), hypertension (none, chronic, or either gestational or eclampsia), diabetes mellitus (none, chronic, or gestational),

TABLE 2
Infertility diagnoses and in vitro fertilization treatment parameters by plurality

Plurality at birth	Singletons				Twins				Triplets+			
Oocyte source-embryo state	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed
N, pregnancies	56,037	16,997	8129	3574	22,858	4686	4921	1041	1359	281	168	55
Prior IVF												
Women with prior cycles, %	54.3	91.7	66.8	89.9	52.1	91.3	68.1	87.2	61.1	92.9	71.3	81.8
Prior cycles, mean (SD)	1.6 (2.2)	2.7 (2.6)	2.5 (2.9)	3.7 (3.5)	1.5 (2.1)	2.4 (2.2)	2.6 (2.9)	3.3 (3.1)	1.8 (2.2)	2.7 (2.3)	2.6 (3.1)	3.4 (3.3)
Diagnoses male factor, %	40.5	40.0	19.7	19.9	42.2	40.1	21.0	19.9	45.3	42.4	29.1	20.0
Endometriosis	12.0	11.7	6.6	6.9	12.9	11.9	6.6	7.4	13.6	13.9	7.2	1.8
Ovulation disorders	15.8	20.1	3.2	4.4	18.2	21.7	4.4	4.5	18.1	24.3	3.2	5.5
Diminished ovarian reserve	16.3	10.6	78.2	77.4	11.2	8.2	77.9	75.8	11.8	6.4	72.5	79.4
Tubal factors	16.1	16.7	6.9	7.8	16.7	17.6	7.6	8.2	19.4	24.3	11.1	9.7
Uterine factors	4.3	4.5	4.8	5.7	3.9	4.1	4.7	5.4	3.8	3.1	3.8	3.6
Other factors	11.8	12.2	16.4	16.6	10.7	11.6	15.5	17.3	10.0	9.6	10.0	12.7
Unexplained	13.7	13.0	3.6	2.9	13.8	13.1	3.6	3.5	12.5	8.6	5.4	1.8
Embryos transferred, %												
1	12.2	24.1	15.3	21.8	0.6	1.9	0.3	1.4	0.3	0.7	0.0	0.0
2	53.1	51.0	70.8	53.4	65.3	63.1	83.5	63.8	26.8	19.8	43.7	14.5
>2	34.8	24.9	14.0	24.8	34.1	35.0	16.1	34.7	73.0	79.5	56.3	85.5
Fetal heartbeats at 6 wk, %												
1	92.0	94.3	89.2	94.1	0.9	1.0	0.5	1.5	0.4	1.3	1.8	0.0
2	7.1	5.2	9.5	5.4	93.5	93.5	95.4	93.6	4.4	1.4	4.6	4.8
>2	0.9	0.5	1.2	0.6	5.6	5.5	4.1	4.9	95.1	97.2	93.6	95.2

IVF, in vitro fertilization.

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

	Singletons						Twins						Triplets+					
			IVF						IVF						IVF			
	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed
N, pregnancies	1,326,650	9142	56,037	16,997	8129	3574	19,116	1951	22,858	4686	4921	1041	352	205	1359	281	168	55
Diabetes, %																		
Pregestational diabetes	0.6	0.9	0.7	0.7	0.8	1.0	0.8	1.0	0.6	0.7	0.7	1.1	0.6	1.0	1.5	0.7	3.0	0.0
Gestational diabetes	4.4	9.2	6.3	6.5	7.6	8.4	5.7	10.0	7.7	8.4	9.5	9.5	8.3	14.5	9.9	9.6	9.2	12.1
Hypertension, %																		
Pregestational hypertension	1.1	2.2	1.4	1.6	2.8	2.6	1.7	2.5	1.3	1.8	3.1	3.5	1.6	1.9	2.0	2.0	3.2	8.5
Gestational hypertension	3.5	6.5	4.2	5.0	8.6	7.4	7.7	11.1	8.8	12.3	18.4	15.4	9.4	16.9	13.4	18.3	29.4	19.9
Preeclampsia	0.2	0.3	0.3	0.2	0.6	0.4	0.6	0.9	0.6	0.6	1.2	0.5	1.2	0.8	0.9	1.2	2.5	0.0
Mode of delivery, %																		
Vaginal	67.6	56.4	54.6	46.3	32.5	31.6	25.2	21.8	18.0	16.2	10.8	12.5	6.9	3.8	4.4	5.9	3.2	1.8
Cesarean	32.4	43.6	45.4	53.7	67.5	68.4	74.8	78.2	82.0	83.8	89.2	87.5	93.1	96.2	95.6	94.1	96.8	98.2
Repeat cesarean	42.4	30.6	21.4	34.1	16.8	36.3	22.4	17.6	12.5	20.3	12.9	26.7	20.2	18.1	12.4	16.8	13.5	24.2
Length of gestation																		
Wk, mean (SD)	38.7 (2.0)	38.4 (2.3)	38.4 (2.2)	38.5 (2.2)	38.2 (2.4)	38.0 (2.4)	35.3 (3.1)	34.9 (3.6)	35.3 (3.0)	35.3 (3.0)	35.3 (2.9)	35.2 (2.9)	31.8 (3.3)	31.8 (3.1)	32.1 (3.2)	32.0 (3.4)	32.1 (2.9)	32.4 (3.2)
<28 wk, %	0.5	1.1	0.7	0.7	0.8	0.8	3.5	5.9	3.3	3.0	2.3	3.0	10.6	10.4	9.8	11.6	7.2	5.6
28–32 wk, %	1.1	1.5	1.7	1.5	2.3	2.8	10.1	12.2	10.4	10.8	11.4	11.5	41.9	40.4	39.1	35.9	44.6	41.4
33–36 wk, %	6.6	8.6	9.0	8.8	12.1	13.3	44.2	41.5	45.0	45.4	48.0	49.8	45.8	47.9	47.7	50.1	44.0	45.7
≥37 wk, %	91.9	88.9	88.5	89.0	84.8	83.1	42.2	40.4	41.3	40.8	38.3	35.7	1.8	1.3	3.3	2.4	4.2	7.4
Infant morbidity																		
NICU admission	6.0	9.3	7.9	8.4	10.4	10.6	31.4	36.4	32.7	31.7	35.6	36.9	73.4	81.1	79.4	75.8	78.5	75.6
Neonatal death	0.2	0.6	0.2	0.3	0.2	0.3	1.3	2.8	1.0	0.9	0.7	1.0	3.9	2.4	2.9	2.6	0.8	1.2
Infant death	0.4	0.6	0.3	0.4	0.3	0.4	1.8	3.1	1.4	1.2	1.1	1.1	4.3	3.2	3.7	3.1	1.4	4.2
Rates of severe maternal morbidity[a]																		
Any morbidity	1179	2477	1875	2141	1993	1427	1297	1863	1251	2017	2205	2210	2812	3152	2011	4513	2786	5455
Admission to intensive care	125	139	182	200	381	420	393	373	335	683	904	721	1433	1778	883	2138	1791	0

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(continued)

TABLE 3
Pregnancy, birth, and infant outcomes by maternal fertility group and plurality at birth *(continued)*

	Singletons					Twins					Triplets+				
			IVF					IVF					IVF		
	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed
Blood transfusion	207	405	312	424	590	559	745	1251	709	1206	1433	1201	1470	1890	1251	2850	1791	5455
Ruptured uterus	31	58	66	65	12	28	73	80	68	43	51	0	0	0	25	238	398	0
Unplanned hysterectomy	33	46	55	159	185	280	122	213	77	277	335	432	92	0	147	356	597	0
Third- or fourth-degree perineal laceration[b]	1231	3477	2506	3205	3254	1596	620	1230	[c]	[c]	[c]	[c]	[c]	[c]	[c]	[c]	[c]	[c]

IVF, in vitro fertilization; *NICU*, neonatal intensive care unit.
[a] Per 100,000 pregnancies; [b] Vaginal births only; [c] Insufficient data.
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parity (nulliparous, 1, or ≥2), mode of delivery (vaginal, cesarean, and repeated cesarean), length of gestation (continuous and as <28, 28–32, 33–36, and ≥37 weeks), and infant sex. 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). Dependent variables included the 5 severe morbidity measures as well as hysterectomy after cesarean, which were calculated by maternal fertility status group, overall as well as for women with a prior birth. Perineal laceration was limited to vaginal births only.

Statistical methods

We modeled the risk of each severe morbidity measure and unplanned hysterectomy after vaginal birth and after cesarean birth using logistic regression as adjusted odds ratios (AOR) and 95% confidence intervals controlling for maternal fertility status, age, race and ethnicity, parity, medical conditions (diabetes mellitus and hypertension), plurality at birth, mode of delivery, state of residence, year of birth, and infant sex. For unplanned hysterectomy, we modeled the risk overall and after a vaginal delivery and after a cesarean delivery. We repeated this analysis limited to women with a prior delivery, additionally controlling for prior mode of delivery. For third- or fourth-degree perineal laceration analyses were limited to singleton vaginal births only and the models included length of gestation. Only models with sufficient sample size are presented in the tables. All analyses were performed using software (SAS, Version 9.4).

Results

The study population included 1,477,522 pregnancies (1,346,118 fertile, 11,298 subfertile, 80,254 IVF autologous-fresh, 21,964 IVF autologous-thawed, 13,218 IVF donor-fresh, and 4670 IVF donor-thawed pregnancies): 1,420,529 singleton, 54,573 twin, and 2420 triplet+ pregnancies. A description of maternal

TABLE 4
Risks of severe maternal morbidity by maternal fertility status

	Intensive care		Blood transfusion		Ruptured uterus		Unplanned hysterectomy		Hysterectomy after cesarean		Third- or fourth-degree perineal laceration[a]	
N, Pregnancies	1,477,522		1,477,522		1,477,522		1,477,522		522,691		942,742	
Outcomes, %	2130	0.14%	3608	0.24%	506	0.03%	611	0.04%	493	0.09%	12,327	1.31%
	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Fertile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Subfertile	0.87	0.58–1.31	1.58[b]	1.23–2.02[b]	1.47	0.67–3.23	1.08	0.55–2.11	0.91	0.43–1.96	2.08[b]	1.79–2.43[b]
IVF autologous-fresh	0.88	0.74–1.06	1.33[b]	1.14–1.54[b]	1.62[b]	1.14–2.29[b]	1.04	0.74–1.48	0.86	0.58–1.28	1.37[b]	1.26–1.49[b]
IVF autologous-thawed	1.22	0.95–1.57	1.94[b]	1.60–2.36[b]	1.39	0.80–2.45	2.80[b]	1.96–4.00[b]	2.76[b]	1.88–4.04[b]	2.10[b]	1.84–2.40[b]
IVF donor-fresh	1.13	0.84–1.52	2.16[b]	1.69–2.75[b]	0.60	0.20–1.78	2.14[b]	1.33–3.44[b]	1.75[b]	1.02–3.01[b]	2.11[b]	1.66–2.69[b]
IVF donor-thawed	1.08	0.67–1.72	2.01[b]	1.38–2.92[b]	0.33	0.04–2.50	2.46[b]	1.33–4.54[b]	2.05[b]	1.03–4.09[b]	1.28	0.79–2.08

Models adjusted for maternal fertility status, age, parity, race and ethnicity, hypertension and diabetes (pregestational and gestational), plurality at birth, length of gestation, and mode of delivery, as well as state and year of birth and infant sex.

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

[a] Limited to singleton vaginal births only, adjusted for all factors in original model, as well as length of gestation; [b] Significantly increased compared to reference group.

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characteristics by fertility group and plurality are shown in Table 1. Women in the fertile group were more likely to be younger, Hispanic, and multiparous, and were less likely to be college graduates compared to the subfertile and IVF groups, which for most characteristics tended to be similar.

The infertility diagnoses and IVF treatment parameters are shown in Table 2. Fewer women using fresh embryos had prior IVF cycles, averaging 52.1–61.1% (using autologous oocytes) and 66.8–71.3% (using donor oocytes). Women using thawed embryos were more likely to have had prior IVF cycles, averaging 91.3–92.9% (using autologous oocytes) and 81.8–89.9% (using donor oocytes). Male factor infertility was the most frequent diagnosis among women using autologous oocytes, regardless of embryo state or plurality, accounting for 40–45% of diagnoses. For women using donor oocytes, diminished ovarian reserve was the most common diagnosis, accounting for 72–79% for diagnoses, regardless of embryo state and plurality. Only 12.2–24.1% of singleton IVF births had a single embryo transferred, 65.3–83.5% of twin births had 2 embryos transferred, and 56.3–79.5% of triplet+ births had >2 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. Subfertile women had the highest rates of gestational diabetes in singleton (9.2%) and twin (10%) births, and any morbidity (2477/100,000 pregnancies) and third- or fourth-degree perineal laceration in singleton and twin births (3477/100,000 pregnancies and 1230/100,000 pregnancies, respectively). Within each fertility group, the rates of third- or fourth-degree perineal laceration were highest among nulliparas (rates for 100,000 pregnancies for fertile, subfertile, and IVF women: nulliparas: 2115, 3990, and 2913, respectively; parity = 1: 593, 1214, and 1075, respectively; and parity ≥2: 229, 273, and 787, respectively) (data not shown). Women with donor-fresh or donor-thawed cycles had the highest rates of pregestational and gestational hypertension within each

TABLE 5
Risks of severe maternal morbidity among women with prior birth by maternal fertility

	Admission to intensive care		Blood transfusion				Unplanned hysterectomy	
Mode of delivery	Cesarean		Vaginal		Cesarean		Cesarean	
N, Pregnancies	250,345		452,953		250,345		250,345	
Outcomes, %	720	0.29%	451	0.10%	937	0.37%	286	0.11%
	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Fertile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Subfertile	0.58	0.25–1.35	2.91[a]	1.38–6.15[a]	1.04	0.58–1.84	0.85	0.27–2.71
IVF autologous-fresh	0.84	0.62–1.15	1.93[a]	1.23–3.01[a]	1.06	0.82–1.37	0.79	0.48–1.33
IVF autologous-thawed	1.37	0.94–1.99	2.99[a]	1.78–5.02[a]	1.74[a]	1.29–2.33[a]	2.31[a]	1.43–3.71[a]
IVF donor-fresh	1.24	0.78–1.97	5.13[a]	2.39–11.02[a]	1.62[a]	1.07–2.45[a]	1.38	0.62–3.06
IVF donor-thawed	0.84	0.39–1.82	5.20[a]	1.83–14.82[a]	1.64	0.94–2.87	2.45[a]	1.06–5.67[a]

Models adjusted for maternal fertility status, age, parity, race and ethnicity, hypertension and diabetes (pregestational and gestational), plurality at birth, length of gestation, mode of delivery, and prior mode of delivery, as well as state and year of birth and infant sex.

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

[a] Significantly increased compared to reference group.

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plurality. Regardless of fertility group, singleton births were more likely to be delivered vaginally, whereas >74% of twins and >93% of triplet+ births were delivered by cesarean. Within each plurality, fertile women were more likely to deliver vaginally.

The results of the logistic regression models of the risks of severe maternal morbidity for the total study population are shown in Table 4, and limited to women with a prior birth in Table 5. Among the total study population, compared to fertile women, the risk of blood transfusion and third- or fourth-degree perineal laceration was increased for subfertile and each of the 4 oocyte source-embryo state IVF groups. The risk of unplanned hysterectomy and hysterectomy after cesarean delivery was increased for the IVF groups with autologous-thawed, donor-fresh, and donor-thawed. Ruptured uterus was elevated for the autologous-fresh IVF group compared to fertile women.

The pattern was similar among women with a prior delivery, with some risks magnified (Table 5). The risk of blood transfusion after vaginal delivery was increased for subfertile and all 4 groups of IVF-treated women; the risk after cesarean was increased for the autologous-thawed and donor-fresh groups. The risk of unplanned hysterectomy was increased for pregnancies from autologous-thawed and donor-thawed cycles.

Comment

Main findings

Defined as unexpected outcomes of labor and delivery that result in significant short- or long-term consequences to a woman's health, severe maternal morbidity affects an estimated 52,000 women annually in the United States.[15,16] These analyses demonstrate that the risks of severe maternal morbidity are increased for subfertile and IVF-treated women, particularly in pregnancies that are not from autologous, fresh cycles. These data suggest that adverse maternal outcomes associated with IVF may be at least in part due to underlying infertility.

In analyses adjusted for potential confounders, the risks of unplanned hysterectomy were highest among pregnancies achieved with thawed embryos (AORs of 2.76 for autologous oocytes and 2.05 for donor oocytes for the total population [Table 4], and 2.31 for autologous oocytes and 2.45 for donor oocytes for parous women [Table 5]).

Clinical implications

In IVF cycles without ovarian hyperstimulation, such as frozen or donor cycles, there is a lower risk of ectopic pregnancy, suggesting that factors influencing the tubal-uterine environment may influence abnormal implantation.[17–19] Unlike autologous-fresh cycles, neither thawed embryo cycles nor donor oocyte involve ovarian hyperstimulation in the recipient woman. Londra et al[19] hypothesize that ovarian hyperstimulation results in a uterine environment that increases the risk of endometrial implantation failure and an abnormally located implantation compared with embryo transfer without ovarian hyperstimulation. While clinical studies have reported better rates of implantation, clinical pregnancy, ongoing pregnancy, and live birth with frozen vs fresh embryo transfers,[11,18,20] these cycles have consistently been associated with increased risks for

placenta accreta and pregnancy-induced hypertension,[12,22] as well as an excess of large-for-gestation birthweights.[21–23] Although our study does not have data on abnormal placentation, the risk of blood transfusion was increased for the subfertile group and all 4 IVF groups in analyses based on the total population (Table 4), and in vaginal births among parous women (Table 5). The risk of unplanned hysterectomy was increased in autologous-thawed and donor-fresh and donor-thawed groups in the total population (Table 4), and after cesarean birth in autologous-thawed and donor-thawed groups among parous women (Table 5).

A consistent finding in IVF- and ART-conceived pregnancies is an increased risk of uterine bleeding and placental complications, regardless of plurality, and a greater risk for blood transfusions.[24–29] Our results confirm the higher risk of blood transfusions in both subfertile and IVF-conceived pregnancies, and greater likelihood of unplanned hysterectomy in IVF-conceived births, particularly in pregnancies that are not from autologous, fresh cycles. In their analysis of all births in Norway in 1999 through 2009, Ebbing et al[27] reported increased risks for velamentous and marginal cord insertions with ART (2-fold for singletons, and 4-fold for twins), and a 20–80% risk of recurrence. The subfertility group in our study, although similar to the IVF group in demographic characteristics, generally showed higher rates of severe maternal morbidity, more consistently in twin and triplet+ births. Unlike IVF cycles, identifying non-IVF ART treatments is challenging, as there is no national registry for these treatments. These women may have received IVF treatment from clinics that did not report to either SART (about 17% of all clinics and 9% of all IVF cycles) or the Centers for Disease Control and Prevention (35 out of 499 clinics in 2015), representing less standardized therapy. They may differ in other ways that were not measured in this study, including socioeconomic, anthropometric, and financial factors.

Higher plurality, which is more frequent in subfertile and IVF pregnancies, is a well-established factor for adverse perinatal outcomes, including greater risks for severe maternal morbidity.[30–33] These risks may be related to over-distention of the uterus due to greater fetal number, as well as factors associated with altered placentation in IVF and ART conceptions. Our prior analyses of twin pregnancies (which were additionally linked to hospital discharge data, as well as birth certificates) have reported a 2-fold increased risk of uterine bleeding and placental complications (abruptio placenta, placenta previa, vasa previa) in subfertile and IVF pregnancies.[34]

Nationally in the United States, cesarean rates parallel advancing maternal age: in 2015, women aged ≥40 years were more than twice as likely to deliver by cesarean as women age <20 years (48.4% vs 20.4%).[1] In 2015, the overall low-risk cesarean delivery rate (cesarean delivery among nulliparous women with full-term singletons in a vertex presentation) was 25.8%, ranging from 16.7% for women ages <20 years to 52.0% for women ages ≥40 years.[1] The use of forceps, vacuum extraction, and vaginal births after cesarean has declined dramatically in recent years.[35,36] The rise in cesarean births has paralleled the rate of peripartum hysterectomy, an indicator of severe postpartum hemorrhage.[37] An analysis of the 1994 through 2007 Nationwide Inpatient Sample showed a 15% overall increase in peripartum hysterectomy, including a 23% increase due to abnormal placentation and a 130% increase due to uterine atony (primarily associated with cesarean delivery).[37] During this time period, the rate of severe postpartum hemorrhage (with transfusion or hysterectomy) has doubled.[38,39] Abnormal placentation (placenta accreta, vasa previa, placenta previa, abruptio placenta, and retained placenta) and postpartum hemorrhage from uterine atony are the leading indicators for peripartum hysterectomy.

Strengths and weaknesses

A common problem in observational studies is unmeasured confounders. As can be seen in Table 1, subjects who underwent infertility treatment (subfertile or IVF) were more likely to be white, non-Hispanic, more educated, and older than the fertile controls. These differences may be indicative of unmeasured confounders, such as income, medical insurance, and prenatal care, which may affect maternal morbidity. Although race, ethnicity, education, and age were included in the logistic models, it is not possible to estimate the effect of the unmeasured confounders on the AORs.

The states reported matches for >90% of the records in the SART CORS database to women who delivered. Misidentifications by the states would have the effect of including non-IVF subjects in the IVF groups; this would reduce the AORs of the IVF groups. Luke et al[40] showed that there is a large underreporting of the use of infertility treatment on the birth certificate. Women who did not report their infertility treatment would be included in the fertile group; this would reduce the AOR of the subfertile group (and of the IVF groups). Therefore, the result of misclassification is to reduce the AORs.

Known limitations of birth certificate data include the unreliability of selected items (eg, maternal weight gain) and the high rate of missing values for other items (eg, father's age and race/ethnicity, maternal height and prepregnancy weight).[1] The validity of 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.[41,42]

A major strength of this study is that the SART CORS data were collected prior to and separately from the vital statistics data, so we expect no differential misclassification of maternal

morbidity with respect to IVF. These findings are subject to several limitations. The low frequency of ruptured uterus has been previously documented in studies evaluating hospital discharge data[43] and the severe morbidity measures on the birth certificate, suggesting difficulty in distinguishing between the diagnoses of a ruptured uterus and uterine dehiscence.[44] A recent comparison of the severe maternal morbidity measures on the birth certificate with *International Classification of Diseases, Ninth Revision* coding in delivery admission hospital discharge data showed that the former are greatly underreported, with sensitivities ranging from 0.11 (blood transfusion in vaginal births) to 0.52 (unplanned hysterectomy after cesarean delivery), and positive predictive values ranging from 0.03–0.90, with highest values for blood transfusion and perineal lacerations.[45]

Conclusion and future research direction

These analyses demonstrate that the risks of severe maternal morbidity are increased for subfertile and IVF-treated women, particularly in pregnancies that are not from autologous, fresh cycles. The findings of >2-fold increased risk of unplanned hysterectomy in thawed IVF cycles warrant further study, particularly given the increasing utilization of frozen embryo transfer including freeze-only cycles. As the characteristics of the childbearing population continue to change, it is important that severe maternal morbidity be monitored and validated on a national basis. ■

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Systematic Review ajog.org

GYNECOLOGY

Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis

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The purpose of this study was to determine whether pregnancies that were achieved via oocyte donation, compared with pregnancies achieved via other assisted reproductive technology methods or natural conception, demonstrate increased risk of preeclampsia or gestational hypertension. Comparative studies of pregnancies that were achieved with oocyte donation vs other methods of assisted reproductive technology or natural conception with preeclampsia or gestational hypertension were included as 1 of the measured outcomes. Abstracts and unpublished studies were excluded. Two reviewers independently selected studies, which were assessed for quality with the use of methodological index for non-randomized studies, and extracted the data. Statistical analysis was conducted. Of the 523 studies that were reviewed initially, 19 comparative studies met the predefined inclusion and exclusion criteria and were included in the metaanalysis, which allowed for analysis of a total of 86,515 pregnancies. Our pooled data demonstrated that the risk of preeclampsia is higher in oocyte-donation pregnancies compared with other methods of assisted reproductive technology (odds ratio, 2.54; 95% confidence interval, 1.98—3.24; $P < .0001$) or natural conception (odds ratio, 4.34; 95% confidence interval, 3.10—6.06; $P < .0001$). The risk of gestational hypertension was also increased significantly in oocyte donation pregnancies in comparison with other methods of assisted reproductive technology (odds ratio, 3.00; 95% confidence interval, 2.44—3.70; $P < .0001$) or natural conception (odds ratio, 7.94; 95% confidence interval, 1.73—36.36; $P = .008$). Subgroup analysis that was conducted for singleton and multiple gestations demonstrated a similar risk for preeclampsia and gestational hypertension in both singleton and multiple gestations. This metaanalysis provides further evidence that supports that egg donation increases the risk of preeclampsia and gestational hypertension compared with other assisted reproductive technology methods or natural conception.

Key words: gestational hypertension, oocyte donation, preeclampsia

Introduced for the first time in the early 1980s, oocyte donation enables women with diminished ovarian reserve, premature ovarian failure, genetic disorders, and surgical menopause to become pregnant.[1-3] In 2012, there were approximately 20,000 attempts at pregnancy with the use of oocyte donation in the United States.[4] This number has been increasing over the past decade.[5] However, several adverse pregnancy outcomes have been correlated with pregnancies that were achieved after successful oocyte transfer compared with other conception methods, such as first-trimester bleeding, preterm birth, low birthweight, and intrauterine growth restriction.[6-9] Hypertensive disorders, such as preeclampsia and gestational hypertension, are other important examples of such complications that usually occur after the 20 weeks of gestation.[7-9]

Hypertensive disorders during pregnancy affect 5—10% of all pregnancies in the United States[10]; gestational hypertension is the most common cause of hypertension in pregnancy. Approximately 15% of gestational hypertension cases proceed to chronic hypertension after pregnancy,[11] and 10—50% of patients who initially are diagnosed with gestational hypertension will be diagnosed with preeclampsia in 1—5 weeks after the diagnosis.[12,13] Pregnancy outcomes of mild gestational hypertension are similar to those of the general obstetrics population.[13,14] However, severe gestational hypertension and preeclampsia are significant causes of maternal deaths each year, along with significant fetal morbidities worldwide.[15-17]

Observations of gestational hypertensive complications among oocyte donation pregnancies were first reported in the late 1980s.[18] However, conclusive evidence for association remains a challenge to substantiate because of intrinsic confounding variables within this patient population. Gestational hypertensive disorders are associated independently with inherent characteristics

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of the recipients of oocyte donation, such as advanced maternal age, primiparity, primary cause of infertility (eg, maternal obesity), and ensuing multiple gestations.[19-25] This is especially a concern when several comparative studies have made little attempt to match for these variables across study populations or adjust for them in their subsequent analysis.

A previous metaanalysis was done to encompass studies that were published before 2010 without any subgroup analyses to control for the confounders.[26] In the past 5 years, there have been many more published studies that investigate the occurrence of hypertensive disorders in oocyte donation pregnancies. Therefore, our objective was to conduct a systematic review and metaanalysis of the existing literature to determine whether the risk of preeclampsia or gestational hypertension was increased in pregnancies that were achieved via oocyte donation, compared with other assisted reproductive technology (ART) methods or natural conception.

Methods

This metaanalysis was conducted according to the Metaanalysis of Observational Studies in Epidemiology guidelines.[27]

Literature search

A literature search was done by the investigators in PubMed, MEDLINE, Embase, and CENTRAL from January 1989 to July 15, 2015. In addition, Google, Google Scholar, and references of selected articles were used to identify other studies. We used the following keywords: preeclampsia, pregnancy-induced hypertension, gestational hypertension, pregnancy complication, egg, oocyte, ovum, donation, and donor.

Eligibility criteria

We included comparative studies that described pregnancies that were achieved through oocyte donation with the subsequent generation of preeclampsia or gestational hypertension as an outcome and compared them with pregnancies that were achieved through other methods of ART or natural conception. *Gestational hypertension* is defined as a new-onset elevated blood pressure (mild, ≥140/90 mm Hg; severe, ≥160/110 mm Hg) after 20 weeks of gestation without proteinuria or end-organ failure.[28] Before 2013, preeclampsia was diagnosed when gestational hypertension was accompanied by proteinuria (≥0.3 g/24 h).[29] In 2013, the American College of Obstetricians and Gynecologists (ACOG) replaced proteinuria as a necessary criterion for preeclampsia diagnosis with signs and symptoms of end-organ injuries.[28] The definitions of *preeclampsia* and *gestational hypertension* that were used for inclusion were based on the regional standards and guidelines in place at the time of each study.

Comorbidities (such as, gestational diabetes mellitus, HELLP (hemolysis, elevated liver enzymes, and low platelet count syndrome), morbid obesity, preterm labor, and multiple gestations) were not exclusion criteria. Abstracts, reviews, case studies, editorials, and noncomparative primary studies were excluded. The studies that had nonspecific "hypertensive disorders" as their outcome were also excluded. No language restrictions were applied.

Quality assessment

The Methodological Index for Non-Randomized Studies (MINORS)[30] was used to assess the quality of nonrandomized studies. This framework consists of 12 items that evaluate a study's validity, methods, and completeness of reporting elements. In the MINORS criteria, a comparative study is assigned a score of 0—2 for each of the 12 items included, for a maximum score of 24. Higher scores are indicative of greater methodologic quality.

Two investigators assessed each study independently and compared their scores afterwards to reach a consensus. If an agreement could not be reached, a third investigator was consulted.

Data extraction

The data from oocyte donation pregnancies, which lasted at least until week 20 of gestation, along with the control group, were extracted in a 2 × 2 contingency table. The data for nonoocyte donation ART (such as, in vitro fertilization, intracytoplasmic sperm injection, and insemination) were collected under the ART label. The data on spontaneous conception groups who did not use any type of assisted reproduction were collected separately under the natural conception label. Another investigator confirmed the extracted data independently. Disagreements were resolved by consulting a third investigator.

Data synthesis

Studies were classified into 4 groups based on their outcomes and control groups: (1) preeclampsia as the outcome and other methods of ART as the control, (2) preeclampsia as the outcome and natural conception as the control, (3) gestational hypertension as the outcome and other ART methods as the control, and (4) gestational hypertension as the outcome and natural conception as the control. It was possible for a study to be assigned to >1 group depending on whether they included both preeclampsia and gestational hypertension as the outcome or both ART and natural conception as the control.

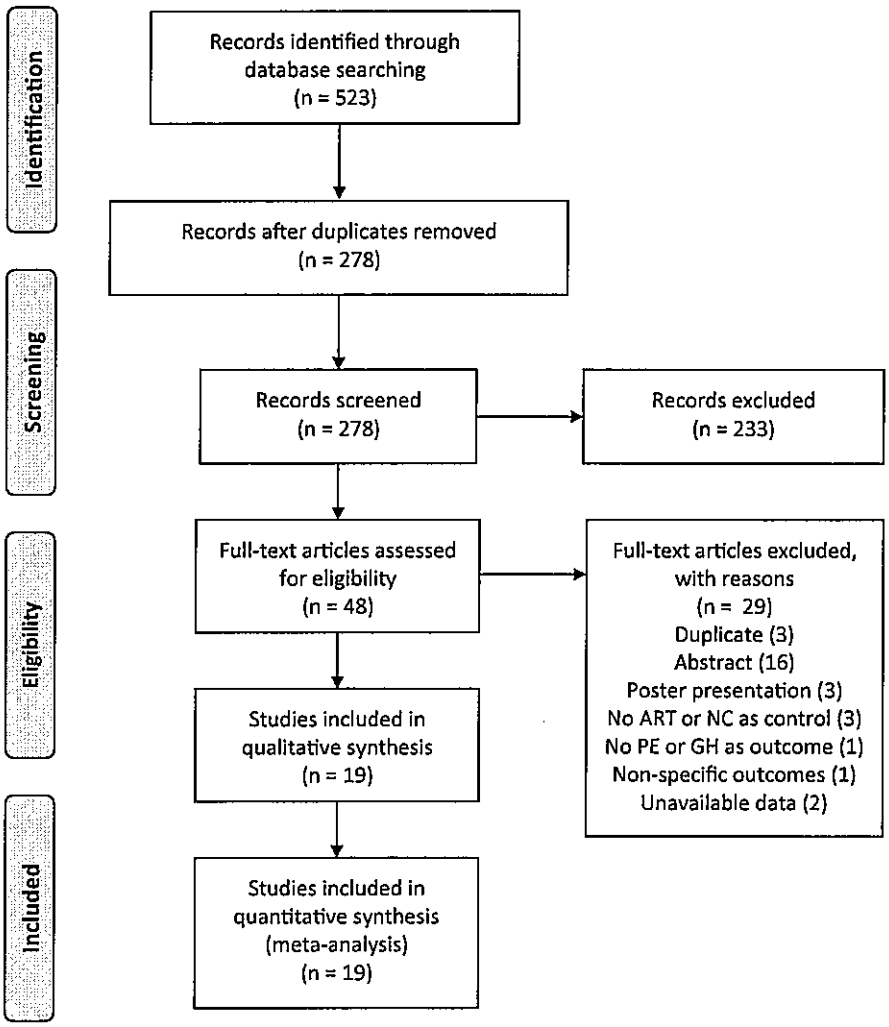
Metaanalysis was performed with Review Manager software (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The Mantel-Haenszel model was used to analyze the dichotomous variables to produce an odds ratio (OR) for each outcome with a 95% confidence interval (CI). For each outcome, the heterogeneity of the study was assessed with the use of Chi^2 test and I^2 statistics. When no degree of heterogeneity was detected ($I^2 = 0\%$), we used a fixed-effects model. When some degree of heterogeneity was present ($I^2 > 0\%$), we used a random-effects model. Funnel plot analysis was used to assess publication bias by plotting ORs against standard errors.

Results

Study characteristics

The conducted search identified 523 studies for initial review, of which 19 were deemed to meet preidentified inclusion and exclusion criteria (Figure 1).[7-9,31-46] There were no randomized control trials found. From the 19 selected studies,

FIGURE 1
Electronic search strategy and results



Flow diagram for inclusion of the studies examining the association between oocyte donation and gestational hypertensive disorders.

ART, assisted reproductive technology; *GH*, gestational hypertension; *NC*, natural conception; *PE*, preeclampsia.

Masoudian. Risk of gestational hypertensive disorders in oocyte donation. Am J Obstet Gynecol 2016.

6 were case-control,[32,33,35,40,41,44,45] and 13 were retrospective cohort studies.[7-9,31,34,36-39,42,43,46] Thirteen studies had other methods of ART as their only comparison[8,9,31-33,35-37,39,42-45]; 3 studies had natural conception as their only comparison,[34,40,46] and 3 studies included both comparison groups.[7,40,41] In regards to outcomes, 5 studies included only preeclampsia[32,34,37,38,40]; 4 studies included only gestational hypertension,[31,33,35,46] and 10 studies included both outcomes.[7-9,36,39,41-45] Ten of the included studies originated from the United States[8,32-37,40,45,46]; 8 originated from Europe,[7,9,31,38,41-44] and 1 originated from Israel.[39] A total of 86,515 pregnant women were included and observed during their pregnancies. The characteristics of the patients in the studies are listed in Table 1. The range of maternal age in the oocyte donation, other methods of ART, and natural conception groups were 33.5-46.2, 33-44, and 30.7-44.1, respectively. One study included only singleton pregnancies[39]; 2 studies that only included twin or multiple pregnancies,[8,32] and 16 studies that did not have such restrictions.[7,9,31,33-38,40-46] Of the 16 studies, 6 studies provided separate data for singleton and multiple subgroups.[7,31,42-45]

Risk of bias in included studies

All 19 studies were assessed for methodologic quality with the use of MINORS criteria (Table 2). There was high concordance between the 2 reviewers; as a result, a third reviewer was involved in only a few instances. Criteria that received a low score in the majority of studies that were assessed included "prospective collection of data" (0% of studies included this), "unbiased assessment of the study endpoint" (5% of studies included this), and "prospective calculation of study size" (5% of studies included this). The remaining 9 criteria were reported by most studies with various degrees of adequacy. Overall, the total MINORS scores of the studies were similar, ranging from 14–20, with a median score of 17.

To identify evidence of publication bias, we generated funnel plots of the studies that used other methods of ART as the comparison group (Figure 2). All included studies fell within the 95% confidence interval lines. Both graphs look symmetric, which indicates no publication bias. Funnel plots for studies with natural conception as comparison group were not generated because of the low number of studies.

Outcome analysis: preeclampsia

There were 15 studies that reported preeclampsia as their outcomes in comparison with in vitro fertilization or intracytoplasmic sperm injection. After pooling the data for metaanalysis, we found that oocyte donation significantly increases the risk of preeclampsia compared with the other methods of ART comparison group (OR, 2.54; 95% CI, 1.98–3.24; $P < .0001$; Figure 3, A). Analysis of the 5 studies that included natural conception as their comparison group also found an increased risk of development of preeclampsia in the oocyte donation patients (OR, 4.34; 95% CI, 3.10–6.06; $P < .0001$; Figure 3, B). A subgroup analysis was performed to examine the effects of singleton vs multiple gestations in the oocyte transfer

TABLE 1
Characteristics of the studies that were included in the metaanalysis

Study	Country	Design	Study period	Inclusion criteria	Exclusion criteria	Control group	Mean maternal age, yr	Parity
Cobo et al,[32] 2014	Spain	RC	2007-2012	Live birth or stillbirth ≥24 weeks of gestation; IVF with own oocyte or donated oocyte	Pregnancy loss at <24 weeks of gestation	IVF	OD, 41.2; ART, 35.7	N/A
Fox et al,[33] 2014	United States	RCC	2005-2012	Twin, >20 weeks of gestation	Monochorionic monoamniotic placentation, previous diagnosis of hypertension	IVF	N/A	N/A
Gundogan et al,[34] 2010	United States	RCC	2004-2006	Placental deliveries with OD	<24 weeks of gestation	IVF	OD, 43; ART, 37.3	N/A
Henne et al,[35] 2007	United States	RC	1997-2002	OD pregnancies	N/A	NC	OD, 42.3; NC, 36.8	OD, 0.59; NC, 1.22
Keegan et al,[36] 2007	United States	RCC	1999-2003	OD/IVF patients <35 or ≥40 years old	Triplet pregnancies, frozen embryo transfers, monitored at program satellite offices	IVF	OD, 42.6; ART, 35.1	N/A
Klatsky et al,[37] 2010	United States	RC	1998-2005	OD pregnancies	N/A	IVF	OD, 40.2; ART, 39.8	OD, 0.27; ART, 0.24
Krieg et al,[38] 2008	United States	RC	2001-2005	OD pregnancies at >38 years old	N/A	IVF	OD, 42.7; ART, 41.3	OD, 0.32; ART, 0.35
Le Ray et al,[39] 2012	France	RC	2008-2010	Women who gave birth at >43 years old	N/A	IVF, NC	OD, 46.2; ART, 44.0; NC, 44.1	OD, 0.3; ART, 0.9; NC, 1.4
Levron et al,[40] 2014	Israel	RC	2005-2011	OD pregnancies beyond first trimester; singleton	Congenital anomalies and chromosomal abnormality	IVF	OD, 45; ART, 41	Nulliparous: OD, 51%; ART, 44%
Malchau et al,[7] 2013	Denmark	RC	1995-2010	OD pregnancies resulted in birth	N/A	IVF, ICSI, NC	OD, 37.1;ART, 33.4; NC, 30.7	OD, 1.3; ART, 1.39; NC, 1.85
Porreco et al,[41] 2005	United States	RCC	1998-2004	OD pregnancies at >45 years old	N/A	NC	N/A	N/A
Salha et al,[42] 1999	UK	RCC	1992-1997	Pregnancies with gamete donation delivered at ≥24 weeks of gestation	N/A	Insemination, embryo donation, NC	OD, 38.1; ART, 31.9; NC, 37.2	Primigravida: OD, 85%; ART, 89%; NC, 82%
Sekhon et al,[8] 2014	United States	RC	2005-2013	Twin, at >24 weeks of gestation	Monochorionic monoamniotic placentation	IVF	OD, 43; ART, 41.9	Nulliparous: OD, 71.1%; ART, 73.1%

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(continued)

TABLE 1
Characteristics of the studies that were included in the metaanalysis *(continued)*

Study	Country	Design	Study period	Inclusion criteria	Exclusion criteria	Control group	Mean maternal age, yr	Parity
Söderström et al,[43] 1998	Finland	RC	1991-1996	OD pregnancies with birth at ≥24 weeks of gestation or ≥500-g newborn infant	N/A	IVF	OD, 33.5; ART, 33.4	Primipara: OD, 84%; ART, 69%
Stoop et al,[44] 2012	Belgium	RC	1999-2008	OD pregnancies with birth at >20 weeks of gestation	Pregnancies after preimplantation genetic diagnosis, testicular sperm extraction, or use of donor sperm	IVF	OD, 36; ART, 36	OD, 0.23; ART, 0.23
Tranquilli et al,[9] 2013	Italy	RC	not specified	26 cases of ICSI embryo transfer with OD	N/A	ICSI	OD, 42.7; ART, 37.5	N/A
Van Dorp et al,[45] 2014	Netherland	RCC	1992-2009	OD pregnancies with birth at >24 weeks of gestation	Cycles without embryo transfer	IVF	OD, 36.4; ART, 36.7	Nulliparous: OD, 78%; ART, 64%
Wiggins and Main,[46] 2005	United States	RCC	1999-2004	OD pregnancies	N/A	IVF	OD, 41.9; ART, 37.7	Nulliparous: OD, 70%; ART, 74%
Wolff et al,[47] 1997	United States	RC	1992-1995	OD pregnancies	N/A	NC	OD, 41.5; NC, 42.7	Nulliparous: OD, 70%; NC, 39%

ART, assisted reproduction therapy; *ICSI*, intracytoplasmic sperm injection; *IVF*, in vitro fertilization; *N/A*, not available; *NC*, natural conception; *OD*, oocyte donation; *RC*, retrospective cohort; *RCC*, retrospective case-control.

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pregnancies with the use of other methods of ART as the comparison. The risk of the development of preeclampsia after oocyte donation was higher in both singleton (OR, 2.24; 95% CI, 1.42–3.53; $P = .0005$; Figure 4, A) and multiple (OR, 2.56; 95% CI, 1.84–3.58; $P < .0001$; Figure 4, B) gestation groups. A sensitivity analysis was done for studies with ART as a comparison, which scored >18; our results were robust (OR, 2.75; 95% CI, 1.93–3.90; $P < .0001$).

Outcome analysis: gestational hypertension

In 13 studies, ART was the comparison group, and gestational hypertension was the outcome. The metaanalysis indicated that oocyte donation pregnancies are at higher risk of gestational hypertension compared with other methods of ART pregnancies (OR, 3.00; 95% CI, 2.44–3.70; $P < .0001$; Figure 5, A). Only 2 studies with gestational hypertension as an outcome had a comparison group that consisted of women with natural conception pregnancies. However, the risk of gestational hypertension was also shown to be higher in the oocyte-donation pregnancies compared with the natural conception group (OR, 7.94; 95% CI, 1.73–36.36; $P = .008$; Figure 5, B). A subgroup analysis of singleton and multiple pregnancies with other methods of ART as the comparison group was conducted. The risk of the development of gestational hypertension was higher in both singleton (OR, 2.86; 95% CI, 2.10–3.90; $P < .0001$; Figure 6, A) and multiple (OR, 3.08; 95% CI, 1.95–4.87; $P < .0001$; Figure 6, B) gestation groups. A sensitivity analysis was done for studies with ART as comparison, which scored >18; our results were robust (OR, 1.93; 95% CI, 2.35-4.33; $P < .0001$).

Comment

Main findings

The main findings of this study indicate that pregnancies that are achieved via oocyte donation have higher risk of the development of preeclampsia and gestational hypertension compared with pregnancies that are achieved through other methods of ART and

natural conception. Subgroup analysis of singleton and nonsingleton gestations was in accordance with the main findings because the risk of the development of preeclampsia and gestational hypertension was still significantly higher than the comparison ART group.

The only systematic review and metaanalysis that has been done to evaluate hypertensive complications in oocyte donation pregnancies was done by Pecks et al.[26] It included 11 observational studies that were published from 1997 to early 2010, 9 of which are also included in our current metaanalysis. Of the 2 studies that were not included, 1 was an abstract,[47] and the other did not differentiate between different kinds of hypertensive disorders.[48] Although the previous metaanalysis included separate analyses for the 2 comparator groups (other methods of ART and natural conception), it did not differentiate between the hypertensive outcomes (gestational hypertension and preeclampsia). Pecks et al also found an association between oocyte donation and hypertensive disorders (OR, 3.87; 95% CI, 2.61–5.74). However, the method of study selection could have been more elaborate, and more parameters could have been included in the

TABLE 2
Methodological Index for Non-Randomized Studies score of the studies that were included in the metaanalysis

Study	Methodological Index for Non-Randomized Studies score
Cobo et al,[32] 2014	18
Fox et al,[33] 2014	17
Gundogan et al,[34] 2010	14
Henne et al,[35] 2007	18
Keegan et al,[36] 2007	15
Klatsky et al,[37] 2010	20
Krieg et al,[38] 2008	15
Le Ray et al,[39] 2012	18
Levron et al,[40] 2014	17
Malchau et al,[7] 2013	16
Porreco et al,[41] 2005	17
Salha et al,[42] 1999	17
Sekhon et al,[8] 2014	20
Söderström et al,[43] 1998	18
Stoop et al,[44] 2012	19
Tranquilli et al,[9] 2013	15
Van Dorp et al,[45] 2014	17
Wiggins and Main,[46] 2005	18
Wolff et al,[47] 1997	16

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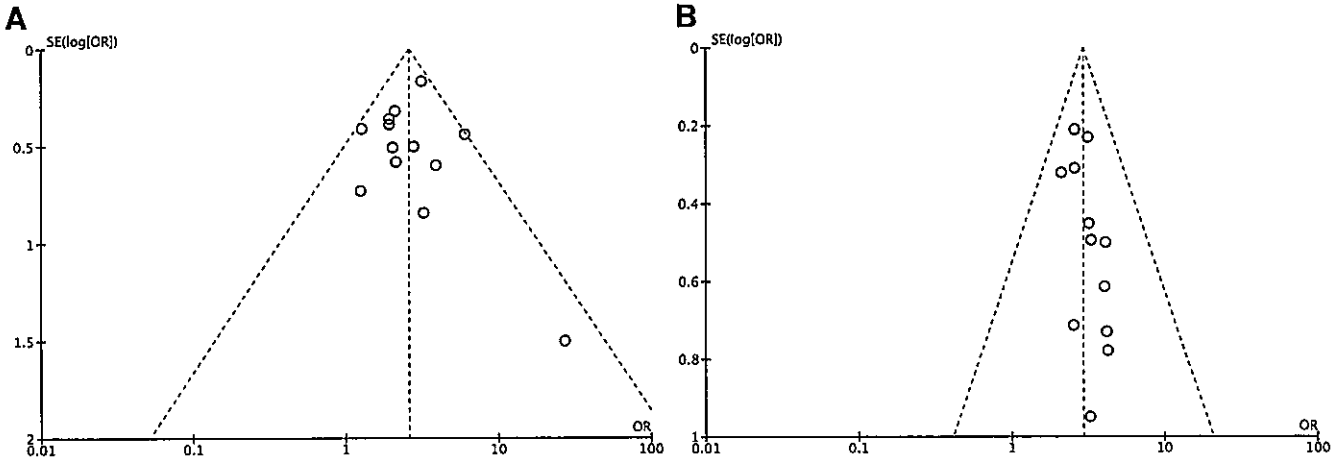
FIGURE 2
Funnel plot of included studies with other methods of assisted reproductive technology



Studies with other methods as the comparison group and A, preeclampsia or B, gestational hypertension as the outcome.

OR, odds ratio; *SE*, standard error.

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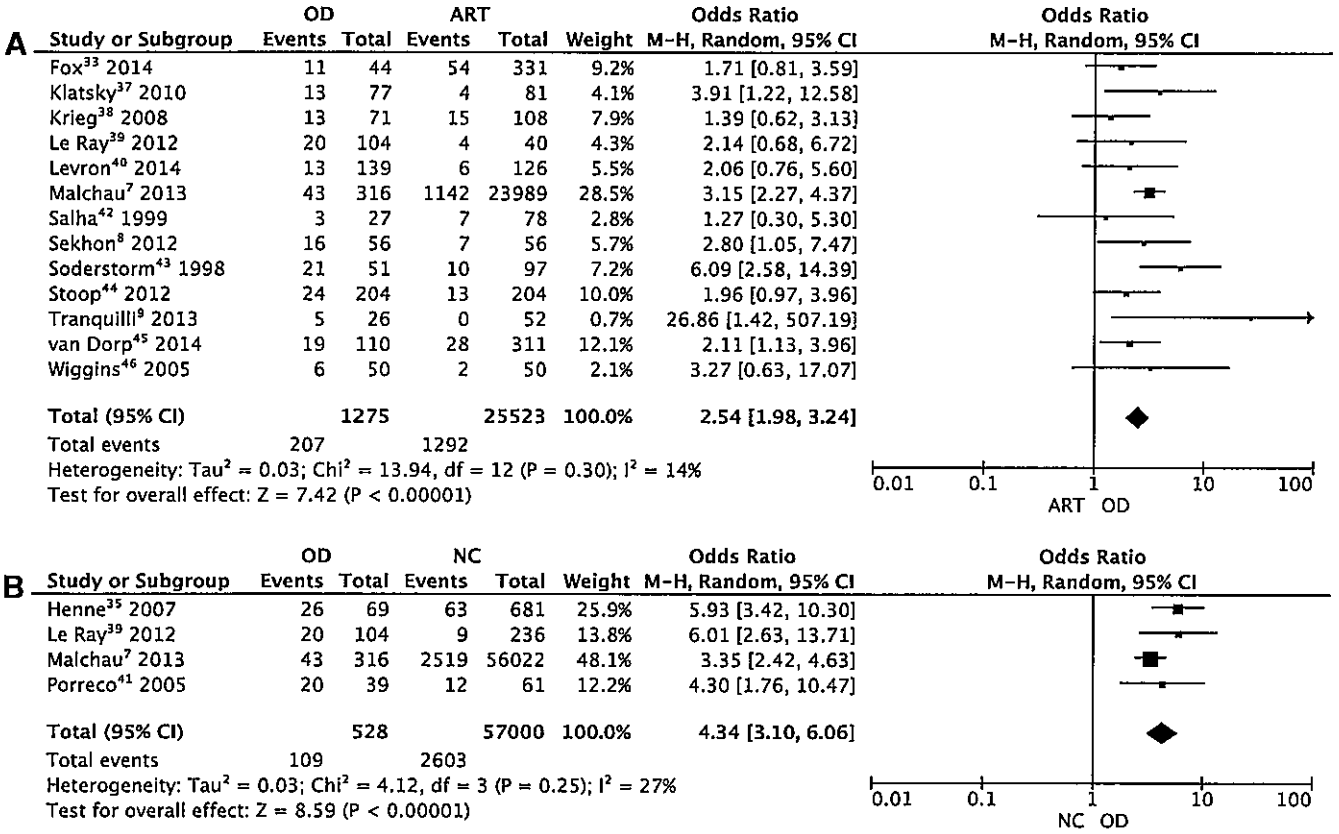
FIGURE 3
Forest plot that compares the risk of preeclampsia outcome in oocyte donation pregnancies



The risk of preeclampsia outcome with **A**, other methods of assisted reproductive technology or **B**, natural conception.

ART, assisted reproductive technology; *CI*, confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel; *NC*, natural conception; *OD*, oocyte donation.

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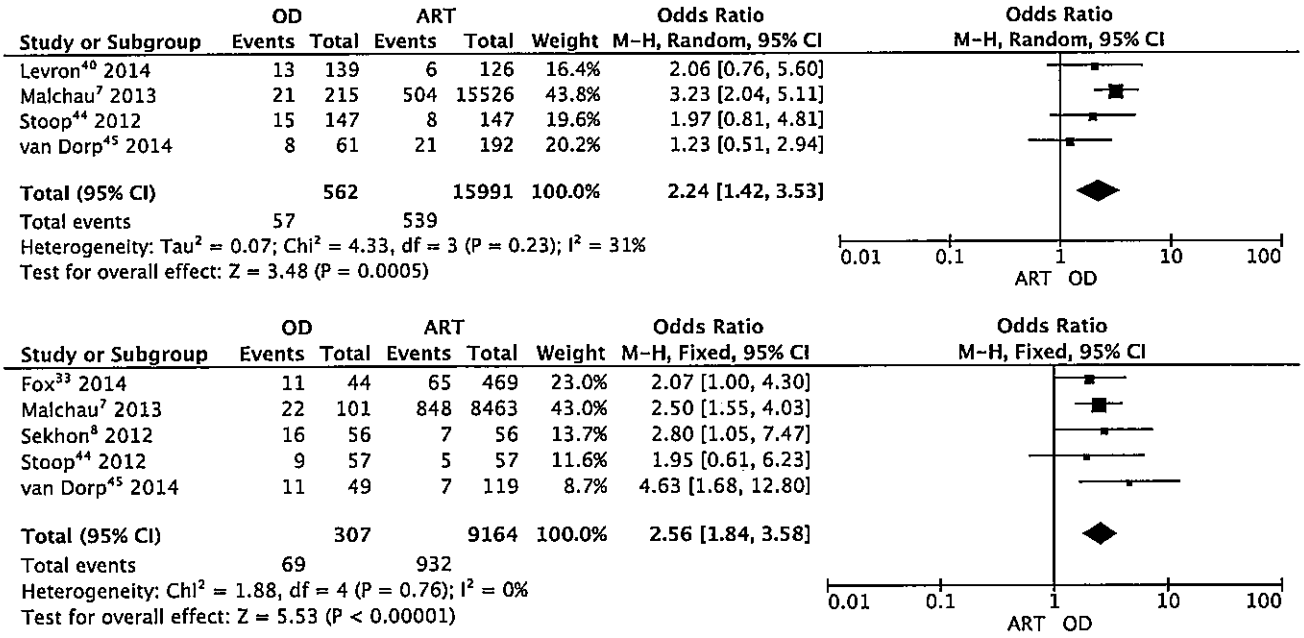
description of the study characteristics (such as sample size, parity, and multiple gestations). Further, there was no of risk of bias assessment of the selected studies included in this publication.

To conclusively identify the independent risk of hypertensive disorders of pregnancy originating from oocyte donation, consideration of the important confounders in this patient population to this outcome must be identified and appropriately accounted for. Pecks et al[26] performed a qualitative assessment of the included studies and concluded that the increased risk of hypertensive disorders in patients with oocyte donation was independent of maternal age and multiple gestations. The quantitative subgroup analysis that was presented in the current analysis supports this conclusion in relation to the number of fetuses being carried in a given pregnancy, whereas insufficient data were available to perform a similar subgroup analysis on maternal age. However, the additional 10 studies[7-9,31,32,36,38,39,43,44] (2010–2014) that were included in the current analysis used appropriate study designs that matched for potential confounders (such as maternal age, parity, and multiple gestations); in cases where this was not possible, the effect of these confounding variables were accounted for with the use of adjusted OR analysis. Although alterations in hormonal milieu could also contribute to the increased risk of preeclampsia and gestational hypertension, the comparison between ART that used autologous oocytes and donor oocytes provides evidence that the introduction of a foreign egg is a major contributing factor. As such, the cumulative data collected to date may support oocyte donation as an independent risk factor for development of preeclampsia and gestational hypertension.

Biologic plausibility

From a biologic standpoint, it is certainly plausible that oocyte donation in and of itself may be an independent risk factor for the development of gestational hypertensive disorders, particularly preeclampsia. The introduction of a foreign egg into the uterus may cause heightened immunologic responses within the recipient and impair the process of placentation.[49-52] Although the cause of preeclampsia is not understood entirely, it is clear that the placenta plays a central role in development of this disorder. In the widely described "2-stage" model of disease, it is believed that placental damage and dysfunction early in pregnancy (<20 weeks of gestation) results in

FIGURE 4
Subgroup forest plot analysis that compares the risk of preeclampsia outcome



The risk of preeclampsia outcome in A, singleton or B, multiple gestations after oocyte donation compared with singleton or multiple gestations after other methods of assisted reproductive technology.

ART, assisted reproductive technology; *CI*, confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel; *NC*, natural conception; *OD*, oocyte donation.

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the release of antiangiogenic and proinflammatory mediators from the placenta into the maternal circulation.[53] This translates a placental disease into the maternal compartment, where it can lead to heightened maternal inflammatory responses and endothelial dysfunction that result in increased peripheral vascular resistance.[54]

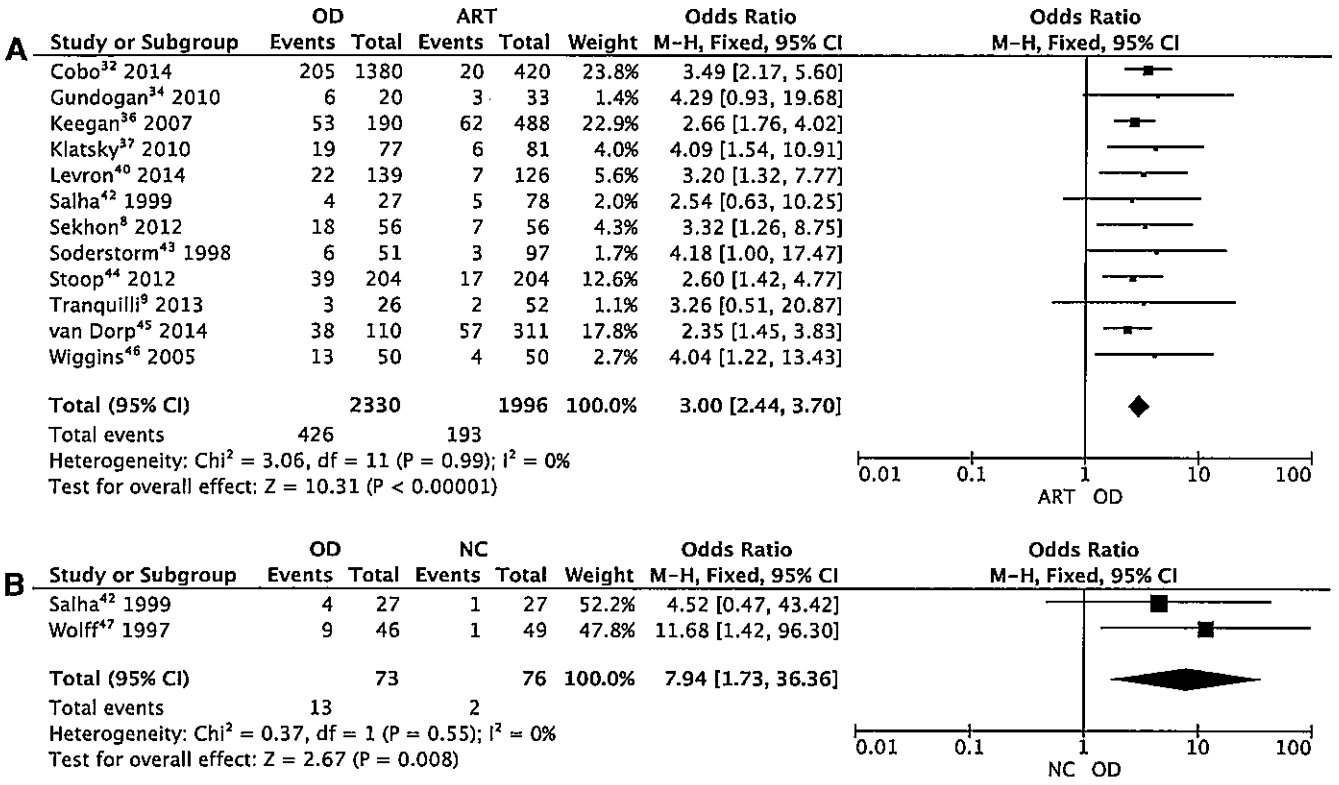
The proposed "immunologic theory" of preeclampsia additionally is supported by evidence of increased preeclampsia risk in pregnancies after sperm donation or previous barrier method contraception use. Similar to the hypothesis provided earlier, in these studies it is postulated that a lack of maternal immune tolerance to paternal sperm antigens generates a heightened immune response at the maternal-fetal interface, which results in placental dysfunction and subsequent preeclampsia.[55-58] Although they are recognized as 2 different diseases, preeclampsia and gestational hypertension have many placental pathologic features in common.[59] Hence, the heightened immune response potentially could play a role in the development of gestational hypertension as well. Considering the evidence presented in this metaanalysis on the risk of preeclampsia and gestational hypertension in these pregnancies, further prospective studies must be conducted to investigate clues and markers of preeclampsia during early pregnancy to provide better opportunities for therapeutic interventions and prevent progression to further stages of the disease.

Strengths and limitations

The strengths of this study include (1) rigorous methodologic systematic review in accordance with Metaanalysis of Observational Studies in Epidemiology guidelines[27]; (2) a comprehensive search of various databases with no language restrictions; (3) the inclusion of a large number of studies with a total of 86,515 pregnant women; (4) a quality assessment of included studies with MINORS criteria to evaluate the risk of study bias[30]; (5) separation of preeclampsia and gestational hypertension as 2 different outcomes because of the difference in pathophysiology, complications, prognosis, and management; (6) separation of other methods of ART and natural conception as 2 different comparison groups, which accounted for the potential difference in the baseline patient characteristics and potential risks of the development of complications; (7) the completion of a subgroup analysis of singleton and nonsingleton pregnancies that did not alter the conclusion; (8) a low degree of heterogeneity that allowed more reliable pooled data; and (9) a lack of publication bias because of the symmetry of the funnel plot.

This study also has some potential limitations. First, all included studies were either retrospective cohort or case control studies. There were no prospective studies or randomized control trials available. This resulted in lower quality assessment scores with the use of the MINORS checklist, which is indicative of a higher risk of bias inherent in the

FIGURE 5
Forest plot that compares the risk of gestational hypertension outcome



The risk of gestational hypertension outcome in oocyte donation pregnancies compared with **A**, other methods of assisted reproductive technology or **B**, natural conception.

ART, assisted reproductive technology; *CI*, confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel; *NC*, natural conception; *OD*, oocyte donation.

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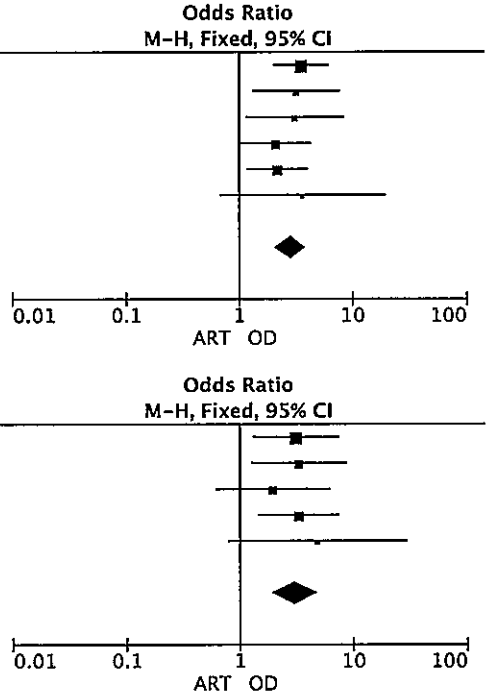
included studies. The lack of prospective studies in this metaanalysis may be the product of restricted key terms that were searched looking for studies that specifically investigated oocyte-donation pregnancies. Therefore, it limited the capture of larger prospective studies with substantial subsets of oocyte-donation pregnancies. One of the initiatives going forward would provide opportunities for future studies to perform a secondary analysis of such potential subsets.

Second, in 2013, ACOG changed the diagnostic criteria for preeclampsia.[28] In the new criteria, the presence of proteinuria can be replaced by new onset of 1 of the following 5 events: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms. Because the cohorts of patients that were studied in most of the studies gave birth before 2013, the diagnostic definition of preeclampsia that was used in the identification of these patients is entirely reflective of the older diagnostic criteria of de novo hypertension in the presence of proteinuria. Also, there was some regional variability among the studies that provided a definition for preeclampsia. The definition of *preeclampsia* based on various regional and international guidelines has been outlined in the systematic review by Gillon et al.[60] Despite the variability, proteinuria remains a consistent feature among the guidelines. In the studies that were included in our metaanalysis, there are small differences in cut-off value for proteinuria (500 mg/24 h rather than 300 mg/24 h). Even for current practices, the new guidelines by ACOG are not adopted universally into clinical practices, and reaching consensus is difficult. As such, diagnosis of patients would be more challenging, and the applicability of these findings to certain patients who were diagnosed with preeclampsia would become more limited. Nonetheless, a similar risk was observed for gestational hypertension that indicated that these changes to diagnostic criteria might have a minimal impact on the risks that are associated with oocyte donation in relation to the development of hypertension in pregnancy.

Third, the presence of few studies for which natural conception was used as a comparator group prevented us from conducting any subgroup analysis with these patients. However, this was justifiable because of the fact that other methods of ART serve as a better control than natural conception because of similarity in patient demographics

FIGURE 6
Subgroup forest plot analysis that compares the risk of gestational hypertension outcome



The risk of gestational hypertension outcome in **A**, singleton or **B**, multiple gestations after oocyte donation compared with singleton or multiple gestations after other methods of assisted reproductive technology.

ART, assisted reproductive technology; *CI*, confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel; *OD*, oocyte donation.

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that may result in higher baseline risk of adverse pregnancy outcomes.

Fourth, there were some parameters that were not considered or adjusted for by many studies. Therefore, the applicability of the results was limited to a certain degree by the confounders. For example, gestational diabetes mellitus and a history of hypertensive disorders in previous pregnancies are established risk factors for hypertensive disorders during pregnancies that were not matched or adjusted for in most of the studies.

Some of the following parameters were included in a few studies: cryopreservation,[31,36,42] maternal smoking,[31,40,42,43,46] maternal body mass index,[8,31,32,42] ethnicity,[8,9,31,36,40,43,44,46] paternal age,[8,43] pregnancy with donor sperm,[31,38] cause of infertility,[31,42,45] and age of the egg donor.[31,40,43-45] One study found an increased incidence of preeclampsia in oocytes that were cryopreserved, compared with fresh egg donations.[36] However, a later study by Cobo et al[31] investigated the effect of cryopreservation as its primary objective and concluded that it is not associated with any major obstetric or perinatal harm. Body mass index is an established risk factor for hypertension in pregnancy.[61-63] On the other hand, smoking is known to reduce the risk of preeclampsia.[64-67] The studies that mentioned the ethnicity of the subjects had predominantly white participants. The role of paternal age, pregnancy with donor sperm, and age of egg donor is still unclear and could be the subject of further investigations in the future. Although it is important that the confounders be accounted for in the forthcoming studies, the consistency in effect direction and size in this study provides strong evidence that the overall conclusion would most likely remain the same.

Conclusions and implications

This metaanalysis suggests that oocyte donation increases the risk of preeclampsia and gestational hypertension, compared with other methods of ART or natural conception. This risk factor should be considered during preconception counseling to ensure that an informed decision is made. Women who become pregnant after oocyte donation should be under closer surveillance after the 20 weeks of gestation for the development of hypertensive disorders. ■

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ORIGINAL ARTICLE

Retrospective Cohort Study

Outcomes of surrogate pregnancies in California and hospital economics of surrogate maternity and newborn care

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Abstract

AIM: To describe maternity and newborn charges for an economic analysis of surrogate pregnancies on the health care resource utilization.

METHODS: A retrospective chart review of all women identified as being surrogates and the infants born from these pregnancies was performed between January 1, 2012 and December 31, 2013. Selected maternity diagnoses, mode of delivery, duration of hospitalization, and hospital charges were collected together with infants' birth weights, gestational age, length of hospital stay, and hospital charges. Charges associated with the *in vitro* fertilization cycles, artificial insemination, or embryo(s) transfer into the surrogate were not considered in the maternity charges. A ratio contrasting the maternity hospital charges for the surrogate carrier was compared as a ratio to the mean charges for 2540 infants delivered in 2013 after natural

conception and adjusted to the baseline hospital charges for both maternity and newborn care.

RESULTS: Analysis of sixty-nine infants delivered from both gestational and traditional surrogate women found an increased in multiple births, NICU admission, and length of stay with hospital charges several multiples beyond that of a term infant conceived naturally and provided care in our nursery. Among singletons and twins (per infant) hospital charges were increased 26 times ($P < 0.001$) and in triplets charges were increased 173 times ($P < 0.0001$) when compared to a term infant provided care in a normal nursery at our center.

CONCLUSION: Maternity costs for surrogates exceed those of women who conceive naturally, and these costs are especially magnified in women with triplets and multiple births.

Key words: Surrogacy pregnancy; Assisted reproductive technologies; Prematurity; Multiple gestations

Core tip: Surrogate pregnancies result in higher maternity and newborn costs with increased rates of multiple births and creates a moral hazard for hospitals. This increase occurs despite of the fact that surrogate mothers are prescreened for health and reproductive ability. Reduction in multiple embryo transfer would reduce the adverse economic impact of surrogate pregnancy, maternity and newborn costs.

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INTRODUCTION

In the United States approximately 7.4% of married couples are affected by infertility[1]. The causes of infertility are multiple and range from advanced maternal age, uterine malformation, hysterectomy, fallopian tube blockage, previous tubal ligation, lack of oocyte reserve in women, male factor infertility associated with oligospermia, pervious vasectomy with failed reconstruction, and other causes. In addition to fertility, in our evolving society where non-traditional family models are increasingly accepted, more and more single adults, or adults in same-sex relationships or marriage also desire to become parents and rear a family. In many such situations prospective parents may enter into an agreement to obtain oocytes or sperm, or use the surrogate's own egg and serve as a traditional surrogate for a pregnancy[2]. In other situations, a couple that has genetically related embryos created through *in vitro* fertilization (IVF) requires another women, a gestational carrier, in whom an embryo(s) and fetus(es) may develop. After birth, through a contractual relationship arranged prior to pregnancy, the gestational carrier relinquishes the infant(s) to the intended parents[2].

In many countries and in some United States states, traditional and gestational surrogacy is illegal. In the United States and its territories, a patchwork of laws regarding surrogacy exists[3]. Some United States states, limit the use of surrogacy, or permit surrogate pregnancies or use of gestational carriers only among married couples or the use of gametes from relatives, and in most states surrogacy contracts and their enforcement are determined by case law. Nevertheless, surrogacy is gaining greater societal acceptance in the United States. For instance, in California, one of the most liberal United States states in this respect, the law permits both traditional and gestational surrogacy in exchange for payment, and designates independent legal counsel for the surrogate and the intended parents, and the creation of a contract with judicial review and approval under the Uniform Parentage Act as amended in 2012[4]. However, the recruitment of women as traditional or as gestational surrogate carriers is unregulated in California. Further informed consent with thorough discussion of the risks associated with oocyte retrieval for some embryo transfers used in gestational surrogacy is unregulated in all states except California, and significant gaps have been identified in adherence to state statutes[5]. Despite the growing popularity of surrogacy, the medical complications associated with surrogacy and the related costs have not been precisely quantified to date. While anecdotal evidence suggests that these complications and costs are much higher than in normal pregnancies no peer reviewed data are available for documentation. This is a critical question to explore since such complications have not only financial and social costs, but may raise ethical issues for prospective parents, physicians, and hospitals. These issues need to be quantified and clarified, so that proper information and counseling/guidance can be provided to the potential parents and to women wishing to be surrogates.

In 2012, the Society for Assisted Reproductive Technology reported that among 379 of their member clinics, 165172 cycles or procedures involving *in vitro* fertilization were performed, and that infants conceived using *in vitro* fertilization procedures constituted 1.5% of all births in the United States[6]. However, the number of infants being born using either traditional or gestational surrogacy is not known. For 2009, the Centers for Disease Control and Prevention (CDC) released information regarding 145244 assisted reproductive procedures performed

in the United States. California ranked the highest with 18405 procedures performed, with 7545 infants born from the use of these technologies. Only 52.7% of the infants born were singletons - in contrast to 96.8% of naturally conceived infants[7], and these data did not distinguish between surrogate and other IVF births.

IVF pregnancies are considered high-risk pregnancies due to the increased risk of prematurity, pregnancy related complications, and increased incidence of multiple gestations. These factors may directly relate to the increased medical charges associated with these pregnancies[8]. There are multiple costs specific to surrogacy, many of which are beyond the purview of this report, which focuses on the hospital costs associated with surrogate births. For example, the costs of acquisition of surrogate or gestational carrier women (often through the use of agencies who advertise for eligible women), attorneys who specialize in preparing contracts between prospective parents and the surrogate, and other costs such as specialized social services, psychological counseling for the intended parents and often for the surrogate herself.

We hypothesized that hospital charges for maternity and newborn care would be significantly greater for women serving as surrogates than those delivering after natural conception and that the hospital charges for the infants would also be significantly greater than for infants delivered after natural conception and at term among naturally conceived infants. As a major medical center in Southern California we believe that baseline data from our center may be useful in informing those contemplating surrogacy pregnancies.

MATERIALS AND METHODS

The Institutional Review Board of Loma Linda University evaluated this study and determined that it was exempt from informed consent. Selected maternity diagnosis, mode of delivery, duration of hospitalization, and hospital charges were collected from women who were identified by their obstetrical provider as being a surrogate (traditional or gestational carrier). Infants born of these pregnancies had their birth weights, gestational age, length of hospital stay, and hospital charges tabulated, as well as their stay in either the normal nursery or neonatal intensive care unit between January 1, 2012 and December 31, 2013 tabulated from medical chart review. All hospital charges data were independently tabulated by the Office of Finance based on the surrogate's or infant's medical record number, as well as, the source of payment such as private payment, third party insurer, or charged to a national health insurance scheme for international surrogacy arrangements.

Charges associated with the IVF cycles, artificial insemination, or embryo(s) transfer into the surrogate were not considered in the maternity charges. A ratio contrasting the maternity hospital charges for the surrogate carrier was compared as a ratio to the mean charges for 2540 infants delivered in 2013 after natural conception. 2013 was chosen as the baseline hospital charges for both maternity and newborn care, as the electronic medical system and financial accounting system change occurred in late December 2012. Between 2012 and 2013 there was a 9% increase in hospital charges. Therefore hospital charges for both maternity care for 2012 were adjusted by this increase in hospital charges. Charges for infant care in "normal nursery" or in the Neonatal Intensive Care unit were similarly tabulated and charges for 2012 adjusted to charges in 2013 because of the increase in hospital charges.

Table 1 Characteristics of Surrogate Women prior to surrogate pregnancy: mean, range and SD

Surrogates	Age (yr)	Gravidity	Parity
$n = 45$	27	2.7	2.3
Range	20-43	1-8	1-7
SD	4.6	3.6	3.3

RESULTS

According to the CDC, in 2011 and 2012 there were 1766 cycles in gestational carriers in the State of California that resulted in the birth of 1067 infants of whom 36% (in 2011) and 39% (in 2012) were born prematurely. Approximately 15% were multiple births (CDC)[9]. Data from traditional surrogacy pregnancies or outcomes are not collected by either the CDC or by the California Department of Health Services.

At our center, 45 women served as surrogates (24 gestational and 21 traditional) from January 1, 2012 until December 31, 2013. These women averaged 27 (range 20-43) years of age with a mean of 2.7 prior pregnancies prior to being a surrogate during the 24 months of our study (range 0-8 previous pregnancies). These women had an average of 2.3 living children (range 1-7) prior to the surrogate pregnancy. These data (and standard deviations) are summarized in Table 1.

According to maternity documents, prenatal care began in the 4.5 wk of embryo transfer or artificial insemination. Among women delivering at our center with embryo transfers (genetically related or not) 55.5% were with multiple embryos. Sperm from the intended father[7], donor semen[3], or mixed sperm from one male couple were impregnated into the 21 traditional surrogates. The cesarean section rate was 52% for surrogate gestations contrasted to 33% among women who conceived naturally. This increased operative mode of delivery may account for the increased average length of hospitalization among women who were surrogates. Table 2 documents the births as singleton or plural births, surrogate length of stay (LOS) for maternity care pre and post birth, and hospital charges as a ratio to women who delivered after natural conception. In the only triplet gestation

Table 2 Maternal characteristics for surrogate pregnancies related to singleton, twin or triplet delivery

Surrogates	Maternity LOS (d)	Ratio	Hospital charges (± SD)	Ratio
Singleton births (n = 20)	4.2 (1.2)	1.3	$31115	1.2
Twin births (22)	3.5 (0.8)	1.1	$29692 ± 11892	1.1
Triplet births	15	4.7	$102673	3.8

Hospital Length of Maternity Stay (LOS) and charges compare surrogate carrier charges related to LOS and maternity charges for naturally conceived term infants requiring normal nursery care (mean ± SD).

there was a significantly longer length of stay and her maternity charges were considerably higher than compared to either singleton, or twin gestations.

Sixty-nine live-born infants resulted from surrogate gestations. Four infants died soon after birth due to extreme prematurity (although the legalized parents refused resuscitation for 24 wk twins). There was one fetal death in a twin pair, and the surviving infant was classified as a singleton, and among a triplet gestation there was fetal reduction of one fetus, and the infants born were classified as twin. Among the 69 infants born, 78% were born prior to 37 completed wk and 17.4% were born less than 30 wk. The mortality rate was 5.7% among infant born using assisted reproduction technologies in contrast to 0.7% of naturally conceived infants and having their initial admission to the normal nursery. Table 3 documents the infant characteristics by birth weight, gestational age, length of hospitalization, and the ratio of charges compared to naturally conceived infants. Compared to naturally conceived singleton or twin infants admitted to the normal nursery with a mean length of stay of 2.1 d, infants delivered of surrogates had a substantially greater length of stay. This longer length of stay was undoubtedly associated with the greater number of infants admitted to the NICU after delivery to a surrogate. Hospital charges were increased 26 times for both singleton and twin deliveries (tabulated per infant) to surrogates, and 173 times for each triplet infant (the sole triplet set that were born alive).

DISCUSSION

Data regarding outcomes of surrogacy pregnancies in California using a gestational carrier and from our center (both gestational and traditional surrogates) reveal a higher rate of prematurity and lower birth weight than among pregnancies resulting from natural conception. The higher cesarean rate may be explained by the higher multiple gestation pregnancies among surrogates and is consistent with the report on the increasing cesarean section rate among twins[10].

Charges for hospital services for these women and the infants delivered provide new information regarding the consumption of medical services by these pregnancies. A discussion of healthcare economics is relevant to the data presented by our experience at a single center. While many healthcare economic discussions center on dwindling reimbursement, the issue is quite different with provision for services to surrogates. Commercial insurance coverage was available for all but one of the women serving as surrogates, and of the 69 infants all but 8 also had commercial insurance with the other women or infants classified as "self pay" resulting in a net profit for our center for maternity care. Newborns were similarly covered except that national health plans in France and Spain would not cover the costs of neonatal intensive care. Combining a well-insured population with a profitable service line such as neonatal intensive care at our center produces a favorable financial outcome for our center. However, in an environment where state-sponsored insurance payments are declining and more people are migrating towards lower-paying insurance exchanges, medical centers are inclined to protect their major sources of margin. This raises the concern of the "moral hazard" of surrogacy. As illustrated surrogate women and the infants delivered have greater rates of cesarean section, premature birth, and low birth weight infants at significantly higher rates than the population of infants born after natural conception. The same is true for IVF/Assisted Insemination pregnancies[8]. Kissin *et al*[11] recently calculated the increased medical costs attributed to Assisted Reproductive Technologies by state. California led with this economic burden for 2013 estimated at $158800418.

A "moral hazard" occurs when the system that helps create the higher risk pregnancy also stands to profit from the additional care that the women and babies are likely to require. The interests of the 3 decision-making parties - intended parents, healthcare system and insurance system - are not aligned. Although gestational surrogacy represents a fraction of all IVF related births, these increased costs and potential profitability are not aligned with value-based health care. The overwhelming desire of prospective parents is to have a normal infant ideally delivered at term. In most cases, these couples, or even single adults will have attempted multiple other means of having a child before settling on the significantly more complicated method of hiring a surrogate. Most families will be paying cash for the surrogate pregnancy ($20-30000 for a surrogate, if an egg donor is required another $5-10000, the fertility clinic and reproductive endocrinologist $15000 per cycle, the surrogacy agency $10-20000) and attorneys fees of about $10000[12]. However, the cost for prenatal care, maternity charges, and expenses associated with neonatal intensive care may exhaust some intended parents resources. While many intended parents may be able to afford the $50000 or so to begin a pregnancy with the assistance of a surrogate, we have encountered many who have been unprepared for the charges associated with the care of

Table 3 Infant characteristics after birth from surrogate pregnancy

Infant(s)	Birth weight	GA	LOS	Hospital charges	Ratio
Singleton (n = 19)	3798.3 ± 832.9	35.9 ± 2.9	11 ± 3	$154874 ± 326415	26.2
Twins (n = 44)	2151.5 ± 750.5	33.8 ± 4.3	12.7 ± 4	$154885 ± 339442	26.2
Triplets (n = 3)	1337.2 ± 91.8	30.0 ± 0	75.0 ± 0	$1025927 ± 99097	173.8

Hospital charges are expressed as a ratio of hospital charges for per infant compared to hospital charges for a term infant provided care in the normal nursery (mean ± SD). GA: Gestational age; LOS: Length of stay.

a complicated newborn born prematurely and requiring several days in a Neonatal Intensive Care unit. Nor are families necessarily prepared for all the implications of a multiple-birth and the associated short- and long-term costs. If a pregnancy has a lower than normal probability of success or more potential complications how extensive should physicians explain these risks? How much do intended parents need or want to know regarding potential complications in the newborns and the added financial costs associated with a premature infant or multiple births? These questions are central to the ethical debate that has surrounded surrogacy. Kissin *et al*[13] has stressed that outcomes of assisted reproductive technologies should properly be assessed on the basis of the number of singleton infants born at term not simply based on live births.

An extension of the "moral hazard" concerns with surrogacy has been the misunderstandings that arise between intended parents and surrogates, and unforeseen events during such a pregnancy. Intended parents-surrogates disputes have arisen when the intended parents demand that the surrogate terminate a pregnancy when a significant fetal malformation is identified, or intended parents change their mind mid-gestation, *e.g.*, by initiating divorce proceedings, or when an intended parent dies. Surrogates may make greater demands on intended parents when multi-fetal gestations occur, or they may wish to engage in behaviors forbidden in their contract, or they may wish to parent the infant themselves. As noted by Andrew W. Vorzimer, a prominent attorney in arranging such contracts in Los Angeles, of 118 surrogacy cases in which a dispute arose 82 were cases in which the intended parents changes their mind and the remainder were by women serving as surrogates (many of whom were traditional surrogates providing her eggs and also carrying the infant) (Andrew W. Yorzimer, J.D., personal communication July 18, 2013).

Margalit[14], an attorney, argues that surrogacy contracts are both desirable and necessary to ensure fairness and enforceability to the benefit of all parties involved. To increase the likelihood that these dual goals of fairness and enforceability are achieved, Margalit[14] further argues that all parties should have independent legal representation from the start of the process as well as thorough, precise, medical guidance as to the risks and probabilities of various outcomes, including catastrophic outcomes. In addition, the paper argues that both sides should receive social and psychological support, and the contract should comprehensively deal with all possible outcomes, including unhealthy newborn(s), premature birth, complications/chronic diseases, and the divorce/death of the intending parents. Finally, every effort should be made to ensure that the disparity in economic strength between the parties to the contract does not interfere with the parties decision to enter into the contract nor "interferes with their free will". Additional legal/ethical risk may arise when prospective parents turn to off-shore surrogacy agencies (primarily in India, Thailand and Mexico) in an effort to cut costs. While these agencies often charge approximately half of what United States agencies do, some are not as reputable and engage in unethical practices and sometimes out-right fraud[15].

Finally, what is the insurance company's piece of this puzzle? By and large, families have borne the expense of the surrogacy, but the infant is now covered under the family's insurance plan even though the parents have voluntarily assumed more than the usual risk. The health insurance industry has thus far been slow to adjust premiums to risk profiles. However, as responsibility for payment continues to shift over to patients through high-deductible plans and cost-sharing, it's reasonable to expect that voluntary assumptions of greater risk will be looked at more critically by the insurance industry and by state health exchanges that must assume even greater risk.

A potential game-changer to the surrogacy moral hazard is an ongoing shift in how hospitals contract with insurers. Historically, they have been paid on a fee-for-service basis where they are paid a percentage of charges or a per diem rate. As their usage increases so does their payment. Medicare saw tremendous opportunity for abuse under their cost-plus reimbursement in the 70s and switched to a DRG-based case rate that also affects Medicaid (MediCal) hospital payment in California. Recently a number of state Medicaid programs followed suit with All Patient Refined DRG-based case rate payments. However, by and large, providers are still financially incentivized to increase rather than decrease the cost of care.

Increasingly health insurance policies are requiring consumers to be more accountable for their healthcare or they are charged larger premiums.

Another aspect of the "moral hazard" of surrogacy is that voluntary risk acceptance could come increasingly under extreme scrutiny. If a medical center stood not to gain, and rather potentially to lose a great

deal in the care of surrogate women and the infants from these pregnancies (as may occur in some cases of international prospective patents counting on reimbursement from their countries national health plan, especially countries that deem surrogacy illegal) how might this impact the market for the care of women surrogates, or their infants? All of these dynamic considerations make it imperative that prospective parents and medical providers have a full understanding of the risks and frequently unforeseen costs associated with surrogacy decisions.

In conclusion, data from California indicate that gestational surrogacy is increasing, and data highlight the substantial increase in multiple births, often born prematurely in California. We document at our single site the extensive requirement for neonatal intensive care and associated increased hospital charges for medical services for both surrogate (both gestational and traditional) and infants from surrogate pregnancies. In a value-based health care system, the "moral hazard" associated with promotion of surrogacy and the higher charges associated with maternity and infant care raises important issues in an area of health care services lacking regulation.

COMMENTS

Background

Surrogate pregnancies result in increased maternity costs in spite of pre-selected for maternal reproductive health primarily associated with an increase in multiple gestations that are associated with increased cesarean section rates, more preterm deliveries, increased neonatal intensive care with added neonatal morbidities.

Research frontiers

Surrogate pregnancies are permitted in several United States states, but the outcomes of these pregnancies have not been rigorously evaluated in terms of maternity or neonatal complications or hospital associated charges.

Innovations and breakthroughs

California has more surrogate pregnancies of any United States states and the impact on health economics is imperative for healthcare value with significantly greater multiples births than occur have natural conception.

Applications

Health economists and insurance providers are focused on health care value. Given the increased charges associated with surrogate pregnancies and the infants born thereof, surrogacy may come under additional scrutiny because of the moral hazard created by these gestations and the impact on health care resources.

Terminology

In this paper surrogacy includes both traditional and gestational surrogacy.

Peer-review

The authors have performed a good study, the manuscript is interesting.

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Perinatal outcomes after natural conception versus in vitro fertilization (IVF) in gestational surrogates: a model to evaluate IVF treatment versus maternal effects

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Objective: To study the perinatal outcomes between singleton live births achieved with the use of commissioned versus spontaneously conceived embryos carried by the same gestational surrogate.
Design: Retrospective cohort study.
Setting: Academic in vitro fertilization center.
Patient(s): Gestational surrogate.
Intervention(s): None.
Main Outcome Measure(s): Pregnancy outcome, gestational age at birth, birth weight, perinatal complications.
Result(s): We identified 124 gestational surrogates who achieved a total of 494 pregnancies. Pregnancy outcomes for surrogate and spontaneous pregnancies were significantly different ($P<.001$), with surrogate pregnancies more likely to result in twin pregnancies: 33% vs. 1%. Miscarriage and ectopic rates were similar. Of these pregnancies, there were 352 singleton live births: 103 achieved from commissioned embryos and 249 conceived spontaneously. Surrogate births had lower mean gestational age at delivery (38.8 ± 2.1 vs. 39.7 ± 1.4), higher rates of preterm birth (10.7% vs. 3.1%), and higher rates of low birth weight (7.8% vs. 2.4%). Neonates from surrogacy had birth weights that were, on average, 105 g lower. Surrogate births had significantly higher obstetrical complications, including gestational diabetes, hypertension, use of amniocentesis, placenta previa, antibiotic requirement during labor, and cesarean section.
Conclusion(s): Neonates born from commissioned embryos and carried by gestational surrogates have increased adverse perinatal outcomes, including preterm birth, low birth weight, hypertension, maternal gestational diabetes, and placenta previa, compared with singletons conceived spontaneously and carried by the same woman. Our data suggest that assisted reproductive procedures may potentially affect embryo quality and that its negative impact can not be overcome even with a proven healthy uterine environment. (Fertil Steril® 2017;108:993–8. ©2017 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, in vitro fertilization, gestational surrogacy, gestational carrier, perinatal outcome, embryo culture

Past studies have consistently demonstrated that maternal infertility and treatments for infertility are associated with adverse pregnancy outcomes in singleton pregnancies. These include preeclampsia, low birth weight, preterm delivery, placental abruption, and fetal loss (1–5). Mechanisms for the association are unknown. It is thought that poor perinatal outcomes are a manifestation of dysfunctional placentation, which in the infertile population may be attributable to the egg from an infertile woman, the laboratory manipulation of the embryo, or the altered endometrial milieu from ovarian hyperstimulation.

According to Barker's fetal origins of adult disease hypothesis the fetus drives placentation and intrauterine growth (6),

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and nonhuman animal studies suggest that this fetal programming may be influenced by the quality of the oocyte (7). The effect of poor egg quality on obstetrical outcomes is evidenced by the well documented maternal age–related increase in risk for adverse perinatal outcomes (8). We would therefore expect an improvement in perinatal outcomes in donor-oocyte in vitro fertilization (DO-IVF) cycles, which are associated with young age of the oocyte donors and good egg quality. However, epidemiologic analyses reveal perinatal complications similar to those of autologous IVF, including increased rates of gestational diabetes, hypertensive disorders, placental abnormalities, preterm delivery, and caesarean delivery for patients with DO-IVF (9–13). These observations suggest two possibilities. First, that the aging uterine environment (endometrium) plays a more critical role than previously believed. Or second, that assisted reproductive technology (ART) procedures influence the quality of the embryo and subsequent perinatal outcome, regardless of the donor's age.

To better differentiate the influence of the ART-derived embryo and endometrium on perinatal outcomes, we studied a cohort of women who achieved pregnancy via gestational-surrogacy in vitro fertilization (GS-IVF). Because traditional surrogacy (use of the surrogate's own eggs and then carried by the same woman) is rarely implemented now because of ethical and legal concerns, our use of gestational surrogate in this manuscript is interchangeable with gestational carrier. Gestational surrogates preferably have a history of uncomplicated pregnancies and therefore are known to provide a healthy uterine environment; they represent an ideal model to investigate the contribution of the ART-derived embryo to pregnancy outcomes. Furthermore, the recipient's endometrial preparation, consisting of a combination of estrogen and progesterone supplementation, is designed to mimic the natural cycle (14).

Existing literature on perinatal outcomes after GS-IVF is sparse (15, 16). Some authors report lower rates of preeclampsia, low birth weight, and placental abruption in pregnancies achieved through gestational surrogacy compared with conventional IVF (17, 18), implying a protective role of a healthy carrier. However, no studies have compared perinatal outcomes of antecedent pregnancies achieved spontaneously among gestational surrogates with those achieved via ART-derived embryos in GS-IVF (commissioned pregnancies). Use of the gestational surrogate as her own control group allows proper evaluation of the embryo's influence on perinatal outcomes, because factors such as the endometrial environment and confounders specific to the carrier are held constant. We hypothesized that if adverse perinatal outcomes after IVF are primarily due to altered embryo quality, then it should be possible to observe an increase in adverse outcomes in commissioned pregnancies when compared with antecedent pregnancies.

We conducted a retrospective cohort study of women who achieved a live birth via gestational surrogacy and compared birth outcomes with their own spontaneously conceived children.

MATERIALS AND METHODS

This was a retrospective cohort analysis of perinatal outcomes among clinical pregnancies achieved through GS-IVF. Gestational surrogates who achieved clinical pregnancies from commissioned embryos from January 1995 to December 2010 were identified at two large California-based surrogacy agencies (Surrogate Parenting Services [Laguna Niguel] and Center for Surrogate Parenting [Encino]). We also identified gestational surrogates who achieved a clinical pregnancy from January 1990 to December 2014 at the University of Southern California Fertility Center (USC Fertility).

Clinical pregnancies were defined as intrauterine pregnancies with documented cardiac motion on ultrasound. Directors of the surrogacy agencies electronically mailed the informed consent and Health Insurance Portability and Accountability Act authorization forms to all gestational surrogates who met inclusion criteria.

USC Fertility patients who agreed to participate also received a secure electronic survey link. Data on perinatal outcomes were collected both by means of the electronic survey instrument and through a detailed review of medical records. Medical records were obtained from the gestational surrogacy agencies and from USC Fertility. All antecedent pregnancies that were spontaneously achieved by these women were included.

Clinical diagnosis of the different obstetrical and perinatal complications was based on the discretion of the primary obstetrical provider. Because there was a wide range of providers, specific definitions used to establish a diagnosis of obstetrical complication was not obtained and we assumed that standard of care was practiced.

Records were excluded when data on pregnancy outcome were missing in surrogate pregnancies and for higher-order multiples, multifetal selective reduction, and singletons resulting from spontaneous "vanishing twin syndrome." Data on donor egg use also were obtained on patients that had undergone GS-IVF at USC Fertility. All gestational surrogates underwent endometrial preparation with the use of estrogen and progesterone replacement designed to mimic the natural pattern of E_2 in the circulation. Institutional Review Board approval was met before starting the study.

Sample size was calculated assuming an alpha of 0.05, a drop-out rate of 30%, and 90% power to detect a difference of 9% in rates of preeclampsia between spontaneous pregnancies and gestational surrogacy pregnancies. This was based on a rate of preeclampsia in the general population of 3% (19) compared with the published preeclampsia rate in recipients of IVF egg donation of 12% (20). The required sample size was 309 clinical pregnancies.

Statistical analysis was performed with the use of Stata 14 (Statacorp). Perinatal outcome data were compared between surrogate births and births conceived spontaneously by the same woman. To account for correlation between birth outcomes to the same woman and difference in age, we fitted random-effects regression models (linear models for continuous outcomes and logistic models for dichotomous outcomes) with an exchangeable covariance structure, using mother as the random effect and type of birth (spontaneous vs. surrogate) as the explanatory variable. All statistical tests were two sided with a P value of .05 required for statistical significance.

RESULTS

We identified 124 gestational surrogates who achieved a total of 494 pregnancies (312 spontaneous, 182 surrogate). Demographics of the gestational surrogates are summarized in Table 1. Pregnancy outcomes for surrogate and spontaneous pregnancies were significantly different ($P \leq .001$), with spontaneously pregnancies more likely to have resulted in an elective abortion, although miscarriage and ectopic rates were similar (Table 2). Of the total live births achieved, surrogate pregnancies were significantly more likely to result in twin pregnancies: 32% vs. 1%; $P \leq .001$; Supplemental Table 1 (available online at www.fertstert.org).

Of these 494 clinical pregnancies, there were 352 singleton live births with complete data on birth weight and gestational age (71.3%; Table 3). One hundred three of these were achieved with the use of commissioned embryos via gestational surrogacy, and 249 were conceived spontaneously as previous births by the same women.

Surrogate births had lower mean gestational age at delivery (38.8 ± 2.1 wk vs. 39.7 ± 1.4 wk; $P < .001$), higher rates of preterm birth (10.7% vs. 3.1%; $P = .01$), and higher rates of low birth weight (7.8% vs. 2.4%; $P = .02$). Neonates from surrogacy had birth weights that were, on average, 105 g lower ($P = .03$; Table 3).

Surrogate births had significantly more obstetrical complications, including gestational diabetes, hypertension, use of amniocentesis, placenta previa, antibiotic requirement during labor, and cesarean sections (Table 4).

To determine if the effects seen in surrogate pregnancies were due to unknown effects of the infertility condition of the donors, we attempted to compare surrogate pregnancies between patients using autologous eggs versus donor eggs. However, egg donor information was known for only 29 pregnancies (17 donor eggs, 12 autologous eggs). Gestational age was similar for the two groups (38.2 ± 1.6 wk for donor eggs, 38.3 ± 2.5 wk for autologous eggs). Birth weight was 105 g less for donor eggs (3,269 ± 164 g) than for autologous eggs (3,375 ± 530 g), but the difference was not statistically significant.

TABLE 1

Demographics of gestational surrogates (n = 92 women with complete demographics).

Variable	Data
Age (y) at time of surrogacy	33.0 ± 4.7
Gravidity	2.6 ± 1.1
No. of children	2.3 ± 0.9
Race	
White	68
Asian	2
Hispanic	21
Black	3
Other	6
Marital status	
Single	15
Married	85
Highest level of education	
High school	39
College	56
Graduate school	15

Note: Data presented as mean ± standard deviation or percent.

Woo. Gestational surrogacy perinatal outcomes. Fertil Steril 2017.

TABLE 2

Pregnancy outcomes.[a]

Outcome	Surrogacy (n = 182)	Spontaneous (n = 312)
Live birth	177 (97)	277 (89)
Miscarriage	5 (3)	12 (4)
Elective abortion	0 (0)	21 (7)
Stillbirth	0 (0)	1 (<1)
Ectopic	0 (0)	1 (<1)

Note: Data presented as n (%).

[a] Fisher exact test, $P < .001$.

Woo. Gestational surrogacy perinatal outcomes. Fertil Steril 2017.

DISCUSSION

This is the first study to compare perinatal outcomes between live births achieved via ART and gestational surrogacy versus spontaneously conceived pregnancies in the same woman. The purpose of this study was to provide better insight into the influence of ART-derived embryos on perinatal outcomes. With the use of the same woman's antecedent pregnancies as controls for the commissioned pregnancies, factors such as the uterine environment and other confounders related to the carrier are kept constant.

Notably, our study shows that the neonates born from ART-derived embryos had lower mean gestational age, higher rates of preterm birth, and lower birth weights. In addition, the women were more likely to develop gestational diabetes and placenta previa and to deliver by means of cesarean section when carrying ART pregnancies versus their own spontaneously conceived neonates. This supports the theory that the processes involved with ART may have adverse effects on the development of the fetus.

Concerns regarding the potential impact of ART manipulation of gametes and in vitro culture of embryos are not new. Since the first infant in the United States conceived through ART was born in 1981, interests about the health of these neonates have been expressed by the scientific community (21, 22). In 1996, the Centers for Disease Control and

TABLE 3

Perinatal outcomes for singleton live births.

Outcome	Surrogacy (n = 103)	Spontaneous (n = 249)	*P* value
Gestational age (wk)	38.8 ± 2.1	39.7 ± 1.4	< .001
Preterm birth	11 (10.7)	8 (3.1)	.01
Birth weight (g)	3,436 ± 696	3,541 ± 504	.03
Low birth weight	8 (7.8)	6 (2.4)	.02

Note: Data presented as mean ± standard deviation or n (%).

There were 352 singleton live births with complete information regarding birth weight and gestational age.

Woo. Gestational surrogacy perinatal outcomes. Fertil Steril 2017.

TABLE 4

Obstetrical complications for singleton live births.

Complication	Surrogacy (n = 103)	Spontaneous (n = 249)	*P* value
Preeclampsia	2 (1.9)	3 (1.2)	.59
Hypertension	7 (6.8)	7 (2.81)	.03
Gestational diabetes	7 (6.8)	3 (1.2)	.01
Placenta previa	5 (4.9)	3 (1.2)	.05
Amniocentesis	7 (6.8)	0 (0)	< .001
Vaginal bleeding	3 (2.9)	5 (2.0)	.71
Meconium	1 (1.0)	8 (3.2)	.26
Antibiotics required in labor	5 (6.2)	1 (0.5)	.02
Emergency CS	3 (3.5)	6 (2.8)	.77
Total CS	19 (19.0)	18 (8.7)	.01
Postpartum hemorrhage	2 (19.4)	0 (0)	.09

Note: Data presented as n (%).
CS = cesarean section.

Woo. Gestational surrogacy perinatal outcomes. Fertil Steril 2017.

Prevention mandated data collection on ART procedures performed in fertility clinics to monitor outcomes of infants born via ART (23). There is some evidence that laboratory or medical procedures may play a role in the adverse perinatal outcome in ART singletons (24, 25). Specific laboratory procedures, such as incubator systems, type of embryo culture media, duration of culture, intracytoplasmic sperm injection (ICSI), and cryopreservation methods, all may introduce stress to the developing embryo. For example, studies have shown that growing embryos to blastocyst stage may be associated with an increased risk of monozygotic twinning (26, 27).

Evidence also suggests an effect of ART on epigenetics and gene expression. Environmental conditions can lead to modification of gene expression through epigenetic modification of the DNA. Inherent to the use of ART is the manipulation of the microenvironment surrounding the developing embryo. Controlled ovarian stimulation occurs during gametogenesis, ICSI or IVF at fertilization, and culture media and nutrition during early embryonic development; all may alter epigenetic reprograming and affect the fate of the embryo (28). Studies have shown alterations in DNA methylation status of imprinted genes (29), with the large offspring syndrome being the most notorious alteration in phenotype seen in animals produced by IVF (30, 31).

One strength of the present study is our use of antecedent pregnancies as controls to evaluate the effects of ART on human embryos. The use of controls from the general population would not account for laboratory and medical procedures or the effects of infertility on the uterine environment. In infertile patients, undiagnosed uterine factors may contribute to the adverse perinatal outcomes. In a gestational surrogate model, the woman has carried her own healthy pregnancies and thus proved that her uterus, the embryo's microenvironment, is optimal. By means of comparing spontaneously conceived pregnancies and commissioned pregnancies carried by the same women, we can control for the uterine environment and emphasize the contribution of ART techniques used to derive the commissioned embryos.

Women who have had one adverse outcome may be at higher risk of a subsequent adverse outcome. To account for correlated birth outcomes in a single woman, we included a random-effects term for the mother (gestational carrier) in the logistic model (32). This model controls for unmeasured maternal effects that do not change over time. The most relevant time-dependent maternal factor in this study was maternal age at birth. Our results did not significantly change when maternal age was included in the model. However, because maternal age was missing for many of the spontaneous births, results are presented for age-unadjusted models.

Several limitations of our study should be considered. We did not have demographic information, including race, marital status, and education, for ~25% of our surrogates. These are important potential confounders for perinatal outcome. However, because these demographic factors are unlikely to change in a woman who first had her own births and subsequently served as a gestational carrier, we thought that we could include all of these subjects without compromising the validity of our results.

During the period of the study, our clinical practices and laboratory techniques also improved, including transition from slow freeze to vitrification for cryopreservation, sequential to monophasic media, and early two-pronuclei or cleavage transfers to more elective single-embryo transfer of blastocysts. Therefore, we were unable to look at any specific ART technique that may have contributed to the outcome.

Furthermore, it is impossible to distinguish the impact of controlled ovarian stimulation itself versus the embryology laboratory conditions and procedures, such as the culture of the eggs and embryos. Previous studies have noted that ovarian stimulation may negatively affect ART-derived embryos (33, 34), with higher FSH doses associated with lower live birth rates (35). Furthermore, infertility is assumed to be a risk factor for adverse perinatal outcomes in ART singletons (36), although one study showed that even in the same mother an ART singleton has a poorer outcome than the non-ART sibling (37). Ideally, the study of embryos that are derived from healthy egg donors and subsequently carried by a gestational surrogate may help to further isolate the effect of maternal infertility and ART procedures on perinatal outcomes. However, we had insufficient numbers of donor oocyte and surrogate pairs to make an accurate comparison.

Repeated pregnancies themselves may be a contributing factor to the adverse outcomes observed in the commissioned births, although the evidence have been controversial (38, 39). One study showed that in a sibling pair, the IVF/ICSI infant born after a previous spontaneous conception was more likely to have low birth weight and preterm birth (40). However those researchers concluded that the difference in outcomes may be statistically but not clinically relevant. Conversely, another study noted a consistent increase in birth weight from the first to second child independently from mode and order of conception (41). The unique aspect of our study is that these are not true sibling pairs because the previous pregnancies and the commissioned births are not genetically related.

Our study provides additional evidence toward the conclusion that factors related to ART procedures have an influential role in pregnancy, regardless of the carrier uterine

environment. The true physiology behind the poor perinatal outcome observed in association with ART remains unknown, and the magnitude of contribution from ART laboratory manipulation needs further study.

CONCLUSION

This is the largest study to date of gestational surrogates who have given birth to a singleton via surrogacy and the only one evaluating antecedent spontaneous pregnancies achieved by the same woman. Neonates born from commissioned embryos and carried by gestational surrogates have increased adverse perinatal outcomes, including preterm birth, low birth weight, maternal gestational diabetes, hypertension, and placenta previa, compared with the live births conceived spontaneously and carried by the same woman. Our data suggests that the etiology behind the adverse outcomes in ART conceptions is multifactorial, ART procedures may potentially affect embryo quality and/or placentation, and the negative impact can not be overcome even with a healthy proven uterine environment.

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