Journal of Assisted Reproduction and Genetics (2019) 36:1917–1926
https://doi.org/10.1007/s10815-019-01545-3

ASSISTED REPRODUCTION TECHNOLOGIES

Risk of ischemic placental disease is increased following in vitro fertilization with oocyte donation: a retrospective cohort study

Anna M. Modest[1,2] · Katherine M. Johnson[1] · S. Ananth Karumanchi[3,4] · Nina Resetkova[5] · Brett C. Young[1] · Matthew P. Fox[2,6] · Lauren A. Wise[2] · Michele R. Hacker[1,7]

Received: 23 May 2019 / Accepted: 23 July 2019 / Published online: 29 July 2019

Abstract

Purpose Assess the risk of ischemic placental disease (IPD) among in vitro fertilization (IVF; donor and autologous) pregnancies compared with non-IVF pregnancies.

Methods This was a retrospective cohort study of deliveries from 2000 to 2015 at a tertiary hospital. The exposures, donor, and autologous IVF, were compared with non-IVF pregnancies and donor IVF pregnancies were also compared with autologous IVF pregnancies. The outcome was IPD (preeclampsia, placental abruption, small for gestational age (SGA), or intrauterine fetal demise due to placental insufficiency). We defined SGA as birthweight < 10th percentiles for gestational age and sex. A secondary analysis restricted SGA to < 3rd percentile.

Results Of 69,084 deliveries in this cohort, 262 resulted from donor IVF and 3,501 from autologous IVF. Compared with non-IVF pregnancies, IPD was more common among donor IVF pregnancies (risk ratio (RR) = 2.9; 95% CI 2.5–3.4) and autologous IVF pregnancies (RR = 2.0; 95% CI 1.9–2.1), adjusted for age and parity. IVF pregnancies were more likely to be complicated by preeclampsia (donor RR = 3.8; 95% CI 2.8–5.0 and autologous RR = 2.2; 95% CI 2.0–2.5, adjusted for age, parity, and marital status), placental abruption (donor RR = 3.8; 95% CI 2.1–6.7 and autologous RR = 2.5; 95% CI 2.1–3.1, adjusted for age), and SGA (donor RR = 2.7; 95% CI 2.1–3.4 and autologous RR = 2.0; 95% CI 1.9–2.2, adjusted for age and parity). Results were similar when restricting SGA to < 3rd percentile.

Conclusion Pregnancies conceived using donor IVF and autologous IVF were at higher risk of IPD and its associated conditions than non-IVF pregnancies and associations were consistently stronger for donor IVF pregnancies.

Keywords Autologous oocyte · Donor oocyte · Ischemic placental disease · Placental abruption · Preeclampsia · Small for gestational age

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10815-019-01545-3) contains supplementary material, which is available to authorized users.

✉ Anna M. Modest
ammodest@bidmc.harvard.edu

[1] Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center/Harvard Medical School, 330 Brookline Avenue, KS 3, Boston, MA, USA

[2] Department of Epidemiology, Boston University School of Public Health, 715 Albany Street, Boston, MA 02118, USA

[3] Center for Vascular Biology Research, Beth Israel Deaconess Medical Center/Harvard Medical School, 99 Brookline Avenue, RN 359, Boston, MA 02215, USA

[4] Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048, USA

[5] Boston IVF, 130 2nd Avenue, Waltham, MA 02451, USA

[6] Department of Global Health, Boston University School of Public Health, 715 Albany Street, Boston, MA, 02118, USA

[7] Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA

Introduction

Ischemic placental disease (IPD), defined as preeclampsia, placental abruption, and/or small for gestational age (SGA), affects 16–23% of pregnancies in the USA [1–3]. These three conditions can occur separately; however, they often co-occur and have shared risk factors [2, 3]. The etiology of IPD is not well understood, but most hypotheses postulate that abnormal placentation plays a role [4–6]. Specifically, insufficient placentation, or failure of the trophoblasts to properly invade the placental bed, is believed to be the pathogenesis for IPD [6, 7]. IPD contributes to more than half of all medically indicated deliveries before 35 weeks of gestation [3] and half of all preterm births [7].

Several risk factors for IPD have been identified, including advanced maternal age, nulliparity, multiple gestations, chronic hypertension, diabetes (prior to pregnancy and gestational), and a history of one of the conditions of IPD [3, 6, 8–10]. More recently, in vitro fertilization (IVF) has been found to increase the risks of preeclampsia [6, 8, 10–16] and SGA by up to 60% [13, 17, 18]. In addition, IVF pregnancies have been found to have up to five times the risk of placental abruption [8, 11, 12]. Studies assessing differences between IVF using a donated oocyte and IVF using the woman's own oocytes have been mixed in their methodology and subsequent findings [6, 8, 14, 19, 20]. Some have suffered from small sample size, and others have varying comparison groups (such as spontaneous conceptions or autologous IVF). In addition, prior studies have combined outcomes that may not have a shared biological mechanism, such as pregnancy-induced hypertension and preeclampsia. Although the mechanism behind the increased risk of IPD is not clear, one hypothesis pertains to the maternal immunologic response to the pregnancy, which also is thought to be involved in placentation [5, 6, 14]. Maternal immune tolerance is necessary in any pregnancy, given a woman typically shares only half of the genetic material with the fetus [21]. Women who undergo IVF with donor oocytes do not share any genetic material with the fetus, potentially decreasing the immune tolerance needed for an uncomplicated pregnancy [6, 14, 21]. This decreased maternal tolerance to the fetus may lead to a higher risk of abnormal placentation and result in obstetric and neonatal complications [5, 6, 21].

Based on prior work, we hypothesized that the risk of IPD would be elevated among pregnancies conceived with donor oocytes "donor IVF" and a woman's own oocytes "autologous IVF" compared with non-IVF pregnancies. Given the potential immune response to donor oocytes, we also hypothesized there would be an even higher risk of IPD for donor IVF pregnancies compared with autologous IVF pregnancies. To assess these hypotheses, we evaluated the risk of IPD among donor and autologous IVF pregnancies compared with non-IVF pregnancies, as well as the risk of IPD in donor compared with autologous IVF pregnancies.

Methods

Study population

We included all deliveries of live-born infants and intrauterine fetal demise (IUFD) at or after 20 weeks of gestation from January 1, 2000, to June 1, 2015, at Beth Israel Deaconess Medical Center (BIDMC), a large tertiary care hospital. We excluded deliveries to mothers less than 18 years of age. This study was approved by the institutional review boards at Beth Israel Deaconess Medical Center and the Massachusetts Department of Public Health. A summary of data sources used for this study is included in Appendix Table S1.

Exposure

We evaluated three exposure groups: donor IVF, autologous IVF, and non-IVF (reference). Women undergoing either type of IVF could use partner or donor sperm. Oocyte source was abstracted through electronic medical records at Boston IVF, BIDMC's affiliated infertility treatment center, or through the birth certificate data from the Massachusetts Department of Public Health.

Given there was no unique identifier that linked IVF cycles and deliveries, we employed a multi-step approach to match IVF cycles and deliveries using maternal last name, date of birth, and time of conception. First, all IVF cycles (fresh and frozen) performed at Boston IVF from January 1, 1999, to June 1, 2015, with a confirmed clinical pregnancy were identified electronically using clinic-specific procedure codes for IVF type. IVF cycles that ended in an ectopic pregnancy, miscarriage, or induced abortion were excluded.

We determined the first date of the last menstrual cycle from the BIDMC delivery information by subtracting the gestational age at delivery from the date of delivery. Gestational age at delivery is recorded by a clinician based on the best available data in the medical record (first day of the last menstrual period, early ultrasound measures, or IVF dating, as appropriate). To allow for error in gestational age and differences in the length of an IVF cycle, while not capturing a second pregnancy after a potentially failed IVF cycle, we created a 56-day window around last menstrual period (28 days prior to the last menstrual period and 28 days after the last menstrual period). We then used the IVF cycle start date from the Boston IVF data to identify matches where the cycle start date fell within that window and the maternal date of birth and last name were identical. Due to concerns about spelling differences of the name, a second match was done on the remaining cycles without including name, and all matches were confirmed.

The maternal name, date of birth, and date of BIDMC deliveries were sent to the Massachusetts Department of Public Health and matched to birth certificate data.

Pregnancies identified on the birth certificate by maternal report as the result of IVF treatment were included in one of the IVF exposure groups. This would capture IVF pregnancies at other institutions/clinics. Pregnancies not identified as a result of donor IVF were considered to be from autologous IVF. Deliveries that were not identified as resulting from IVF by the Boston IVF data or birth certificate data were considered non-IVF pregnancies.

Outcomes

The outcome was IPD (preeclampsia, placental abruption, or SGA infant) or an IUFD where the cause was classified by the physician as being related to placental insufficiency. SGA was defined as a birthweight below the 10th percentile within strata of gestational age at delivery and infant sex, using a US standard growth curve and was calculated for each infant [22]. A multifetal pregnancy was considered to be affected by SGA if any infant met criteria for SGA. To isolate infants who were more likely to be pathologically small, we used a 3rd percentile cut-off [1, 9] for SGA in a secondary analysis. We could not calculate SGA for all IUFDs' given weight was missing for 170 records and sex was missing for 34 records.

We identified potential cases of preeclampsia using ICD9 diagnosis codes 642.40–642.44, 642.50–642.54, 642.60–642.64, 642.70–642.74, 642.51, and 642.53 and conducted a medical record review to verify the diagnosis. Preeclampsia was defined as the presence of elevated blood pressure (≥ 140/90) during the delivery admission, and either symptoms of preeclampsia (headache, visual changes, severe right upper abdominal pain), seizures, or abnormal laboratory values (proteinuria, alanine aminotransferase/aspartate aminotransferase ≥ 80 units per liter, or platelets < 100,000) before delivery.

We identified potential cases of placental abruption using ICD9 diagnosis codes 641.20–641.23 and also conducted a medical record review to verify the diagnosis. Placental abruption was defined as evidence of abruption or blood clot during a delivery; evidence of abruption on placental pathology; or a very strong clinical suspicion that required hospitalization, intervention, and delivery.

We identified pregnancies that resulted in an IUFD using ICD9 discharge diagnosis codes (656.41, 656.43, V27.1).We reviewed autopsy, pathology, and clinician notes to confirm the IUFD and for documented evidence of placental insufficiency as a possible cause of the IUFD. All work-up for IUFDs was based on clinical judgment and patient consent at the time of the pregnancy.

Due to institutional changes regarding scanned paper records, data sufficient for validation of preeclampsia and placental abruption were only available after July 1, 2008; therefore, we reviewed 59.2% of preeclampsia diagnoses and 53.6% of placental abruption diagnoses. Among the reviewed records, we confirmed 89.3% of the potential preeclampsia cases and 89.7% of the potential abruption cases. Pregnancies after July 1, 2008, where the diagnosis could not be verified, were considered to not have the condition. Given the high accuracy of the ICD9 codes in the later time period, any pregnancy with ICD9 codes for preeclampsia or placental abruption prior to July 1, 2008 was considered to have the complication. AMM and two obstetricians reviewed the medical records. All diagnoses that were unclear were reviewed by a fellowship-trained maternal-fetal medicine physician.

Covariates

Demographic data were self-reported during hospital registration. Obstetric history, including gravidity and parity, and delivery outcomes, including gestational age at delivery, infant sex, and birthweight, were recorded by a clinician at delivery. Information regarding pre-gestational diabetes and smoking prior to pregnancy was self-reported on the birth certificate. Admission to the neonatal intensive care unit (NICU) was calculated based on admission and discharge date and time. For IUFDs, only registration data were available electronically; the remaining data were abstracted from the medical record, when available.

Statistical analysis

We calculated risk ratios (RR) and 95% confidence intervals using log-binomial regression and generalized estimating equations with an independent correlation matrix to account for repeated pregnancies for the same woman. Potential confounders were chosen based on the literature [2], as well as a comparison of covariates that differed by exposure and outcome. Maternal age at last menstrual period was included as a continuous variable in all adjusted models due to the age differences among exposure groups and because age is a strong risk factor for IPD. Each covariate was individually included in the regression model with the exposure and age. The covariate that had the strongest effect on the risk ratio was retained in the model and this process was repeated until no covariate changed the risk ratio by more than 10%. The covariates considered were race/ethnicity (Caucasian or not Caucasian), gravidity (1, 2, 3, or more), parity (0, 1, 2, 3, or more), diabetes prior to pregnancy, smoking prior to pregnancy, marital status, highest level of education, insurance, and year of delivery; they were collapsed into categories due to small sample size in some of the strata.

To evaluate the robustness of our findings and address limitations in the data, we conducted several sensitivity analyses. First, data were restricted to singleton pregnancies, because IVF pregnancies have a higher risk of multiple gestations and pregnancies with multiple gestations also are at higher risk for IPD. We were unable to determine whether women

had a history of IPD, which is a strong predictor of future IPD; thus, a second sensitivity analysis was done restricting to nulliparous women. Finally, in order to evaluate the potential influence of exposure and outcome misclassification due to the inability to verify all of the data, we conducted a probabilistic quantitative bias analysis [23]. The aim of the probabilistic quantitative bias analysis is to quantify the amount of bias in a study and assess what the association between the exposure and outcome would have been without that bias. The bias is quantified using a range of sensitivities and specificities and assumptions about the type of bias (differential or non-differential). Finally, each correction is simulated to test different combinations of sensitivity and specificity. We conducted the bias analysis separately for donor IVF and autologous IVF groups, using the non-IVF group as a common reference group. We used IPD or IUFD with placental insufficiency as the outcome. We assumed non-differential misclassification for the exposure and the outcome; each simulation was run 10,000 times. We used several considerations in our choice of sensitivity and specificity for the bias correction. Due to the affiliation between Boston IVF and BIDMC, we believe that the majority of IVF deliveries at BIDMC would be from cycles performed at Boston IVF. Within our own data, 62% of the IVF cycles identified were from Boston IVF. Furthermore, Boston IVF performs approximately one-third of IVF cycles in the Greater Boston area [24] so we believe that we are capturing a large portion of all of the IVF procedures that are done in the Greater Boston area. With these assumptions, for exposure misclassification, we used a trapezoidal sensitivity distribution (minimum sensitivity 35%, modes at 50% and 70%, maximum 80%). In other words, we assumed that it was most likely to be a sensitivity between 50 to 70%, but allowed variation of anywhere from 35 to 80%. We assumed 100% specificity for exposure because non-IVF pregnancies are unlikely to be misclassified as IVF pregnancies. To evaluate the potential impact of outcome misclassification, we also used a trapezoidal distribution for sensitivity (minimum 60%, modes at 70% and 75%, maximum 80%) and a triangular distribution for specificity (minimum 80%, mode 90%, maximum 95%) based on our medical record review and assuming that, given the severity of the diagnoses and need for obstetric intervention, we would be capturing, and not over diagnosing, the majority of the outcomes.

Results

Baseline demographics

We identified 69,084 pregnancies that were included in this analysis. Of these, 262 (0.4%) were in the donor IVF group, 3,501 (5.1%) were in the autologous IVF group, and 65,321 (94.6%) were in the non-IVF group. Demographic and baseline characteristics for the three exposure groups are presented in Table 1. The three groups differed on several demographic characteristics that are important risk factors for IPD. Women in the donor IVF group were the oldest and those in the non-IVF group were the youngest. In addition, women in the non-IVF group were less likely to be primigravid and nulliparous than their IVF counterparts. Almost all women in both IVF groups had private insurance coverage compared with 84.3% of the non-IVF group.

Delivery outcomes

The median gestational age at delivery was clinically similar across the three exposure groups: 38.0 weeks in the IVF groups and 39.0 weeks in the non-IVF group, although it was statistically significantly different. There was a higher incidence of preterm delivery in the donor IVF (33.2%) and autologous IVF (32.6%) groups compared with the non-IVF group (10.8%; both $p < 0.001$); multiple gestations also were more common in the donor (36.3%) and autologous (32.0%) IVF groups compared with the non-IVF group (2.2%; both $p < 0.001$). IUFDs were rare in this cohort, and there were no differences in the risk of IUFD among the three groups (both $p \geq 0.40$). There were more NICU admissions in both IVF groups (both $p < 0.001$), but there were no meaningful differences in any other neonatal outcomes (Table 2).

Incidence and risk of ischemic placental disease

Overall, 14.2% of the cohort had IPD. More than one-third (36.3%) of the donor IVF group and one-quarter (27.5%) of the autologous IVF group had IPD compared with 13.4% in the non-IVF group. In our adjusted models, we considered race/ethnicity, gravidity, parity, diabetes prior to pregnancy, smoking prior to pregnancy, marital status, education, insurance, and year of delivery as potential confounders. Only confounders that changed the RR by more than 10% were retained in the final models. When adjusted for maternal age and parity, compared with the non-IVF group, the risk of IPD was 2.9 (95% CI 2.5–3.4) in the donor IVF group and 2.0 (95% CI 1.9–2.1) in the autologous IVF group. The risks of each of the components of IPD were higher in the donor IVF and autologous IVF groups compared with the non-IVF group (Table 3). When restricting the definition of SGA to < 3rd percentile, 26.7% of donor IVF pregnancies, 16.6% of autologous IVF pregnancies, and 6.8% of non-IVF pregnancies were affected by IPD. When adjusting for maternal age, parity, and marital status, the risk of IPD was higher among those undergoing donor IVF (RR 3.4, 95% CI 2.7–4.2) and autologous IVF (RR 2.3, 95% CI 2.1–2.5) compared with the non-IVF group. Similar results were seen for the risk of SGA < 3rd percentile.

Table 1 Baseline patient characteristics of deliveries from January 1, 2000, to June 1, 2015, by mode of conception ($n = 69,084$)

	Donor IVF ($n = 262$)	Autologous IVF ($n = 3501$)	Non-IVF ($n = 65321$)
Maternal age (years)	42.3 (39.1–45.1)	35.6 (32.6–38.8)	31.9 (28.6–35.0)
Race			
Caucasian	220 (84.0)	2878 (82.2)	40194 (61.5)
African American	12 (4.6)	131 (3.7)	7915 (12.1)
Asian	12 (4.6)	274 (7.8)	9939 (15.2)
Other	17 (6.5)	215 (6.1)	7031 (10.8)
Not reported/unknown	1 (0.4)	3 (0.1)	242 (0.4)
Marital status			
Married or partnered	232 (88.5)	3276 (93.6)	52745 (80.7)
Single, divorced, separated or widowed	29 (11.1)	219 (6.3)	12015 (18.4)
Unknown/missing	1 (0.4)	85 (2.4)	561 (0.1)
Highest level of education achieved			
Less than high school, high school diploma/GED	16 (6.1)	292 (8.3)	14163 (21.7)
College or associates degree	107 (40.8)	1644 (47.0)	27087 (41.5)
Graduate degree	124 (47.3)	1474 (42.1)	19505 (29.9)
Unknown	15 (5.7)	91 (2.6)	4556 (7.0)
Private insurance	> 258*	3450 (98.5)	55056 (84.3)
Gravidity			
1	150 (57.3)	2061 (58.9)	23706 (36.3)
2	58 (22.1)	733 (20.9)	20947 (32.1)
3+	54 (20.6)	707 (20.2)	20652 (31.6)
Missing	0 (0.0)	0 (0.0)	16 (0.0)
Parity			
0	166 (63.4)	2332 (66.6)	30398 (46.5)
1	72 (27.5)	986 (28.2)	23554 (36.1)
2+	24 (9.2)	183 (5.2)	11366 (17.4)
Missing	0 (0.0)	0 (0.0)	3 (0.0)
Diabetes (prior to pregnancy)	0 (0.0)	81 (2.3)	1028 (1.6)
Smoking (prior to pregnancy)	< 4*	46 (1.3)	2147 (3.3)
Year of delivery			
2000–2003	42 (16.0)	763 (21.8)	14581 (22.3)
2004–2007	72 (27.5)	968 (27.6)	17891 (27.4)
2008–2011	64 (24.4)	868 (24.8)	17591 (26.9)

IVF, in vitro fertilization. Data presented as median (interquartile range) or *n* (%)

*As per Department of Public Health requirements, cell sizes 1–4 cannot be presented, nor can that information be calculated

There was a similar pattern of results when comparing donor IVF pregnancies to autologous IVF pregnancies. Women undergoing donor IVF had a modestly higher risk of IPD (RR 1.5, 95% CI 1.2–1.8) and preeclampsia (RR 2.4, 95% CI 1.8–3.3, adjusted for maternal age) compared with women undergoing autologous IVF (Table 4). While the incidence of placental abruption and SGA was higher in the donor IVF group, the difference was not statistically significant. When restricting the definition of SGA to < 3rd percentile, the donor IVF group had a higher risk of IPD compared with the autologous group (RR 1.8, 95% CI 1.4–2.3) when adjusted for maternal age.

Sensitivity analyses

The results were similar when we restricted the analysis to nulliparous women. The results were attenuated in singleton deliveries, but the risk of IPD was higher in the donor IVF group (RR 2.3, 95% CI 1.8–3.0) compared with the non-IVF group, and modestly higher in the autologous IVF group (RR 1.2, 95% CI 1.1–1.3). (Tables S2-S7) The results of the probabilistic bias analysis show that, given our assumptions, our observed results are an underestimate of the relationship between IVF and IPD or IUFD due to placental insufficiency

Table 2 Immediate pregnancy and delivery outcomes of cohort by mode of conception ($n = 69{,}084$)

Outcomes	Donor IVF ($n = 262$)	p[a]	Autologous IVF ($n = 3501$)	p[b]	Non-IVF ($n = 65321$)
Gestational age at delivery (weeks)	38.0 (35.6–39.0)	< 0.001	38.0 (36.0–39.0)	< 0.001	39.0 (38.0–40.0)
Preterm delivery (< 37 weeks of gestation)	87 (33.2)	< 0.001	1140 (32.6)		7040 (10.8)
Intrauterine fetal demise (IUFD)	0 (0.0)	0.63	12 (0.3)	0.40	287 (0.4)
Gestations		< 0.001		< 0.001	
Singleton	167 (63.7)		2380 (68.0)		63898 (97.8)
Multiple	95 (36.3)		1121 (32.0)		1423 (2.2)
Singletons	$n = 167$		$n = 2380$		$n = 63898$
Sex		0.94		0.64	
Female	81 (48.5)		1173 (49.3)		31184 (48.8)
Male	86 (51.5)		1206 (50.7)		32686 (51.2)
Unknown	0 (0.0)		1 (0.0)		28 (0.0)
Birthweight (grams)	3275 (2800–3660)	0.07	3295 (2925–3625)	< 0.001	3360 (3025–3680)
Multiples[c]	$n = 95$		$n = 1121$		$n = 1423$
Sex		0.002		< 0.001	
Female	25 (26.3)		271 (24.2)		487 (34.2)
Male	23 (24.2)		290 (25.9)		479 (33.7)
Both	47 (49.5)		559 (49.9)		457 (32.1)
Unknown	0 (0.0)		1 (0.1)		0 (0.0)
Birthweight (grams)	2470 (2013–2868)	0.002	2314 (1793–2693)	0.62	2290 (1810–2645)
Admission to NICU[d]		< 0.001		< 0.001	
Yes	100 (38.2)		1141 (32.6)		9717 (14.9)
No	162 (61.8)		2360 (67.4)		55604 (85.1)

IVF, in vitro fertilization; *NICU*, neonatal intensive care unit. Data presented as median (interquartile range) or *n* (%)

[a] *p* values comparing donor IVF and non-IVF

[b] *p* values comparing autologous IVF and non-IVF

[c] Birthweights combined for all infants

[d] Admission defined as at least 4 hours

when we correct for misclassification of the outcome. The observed results are similar to those corrected for exposure misclassification (Table S8), given our assumptions.

Discussion

In the present study, women who conceived with IVF were at higher risk of IPD compared with women who conceived without IVF. In particular, compared with the non-IVF group, women who conceived using donor IVF were almost three times more likely to develop IPD and women who conceived using autologous IVF had double the risk of IPD. These findings persisted when we evaluated the components of IPD (preeclampsia, placental abruption, and SGA) separately. Furthermore, when restricting the definition of SGA to < 3rd percentile, thereby substantially reducing the proportion of constitutionally small babies, the relationship between method of conception and IPD became stronger. Women undergoing donor IVF also had a higher risk of IPD and preeclampsia compared with the autologous IVF group. Our results were robust when restricting the cohort to nulliparous women.

We did see some attenuated risks for SGA when restricting to singleton pregnancies, particularly when using a more stringent definition of SGA (< 3rd percentile). This may be because women with a singleton pregnancy are at lower risk of SGA or restricting may impose a bias. IVF is associated with an increased risk of multiple gestations, which are at higher risk for SGA, and by restricting we are conditioning on a mediator on the causal pathway between exposure and outcome, which we would expect to impose a bias [25]. For similar reasons, we did not adjust for any comorbidity during the pregnancy, such as gestational diabetes.

Our results are consistent with prior literature that shows an increased risk of IPD in IVF pregnancies, as well as an increased risk of preeclampsia in donor IVF pregnancies [6, 14, 16, 19, 20, 26]. In this study, we evaluated the association between type of IVF and risk of IPD as a group of biologically related conditions. Our results support the hypothesis that there are multiple mechanisms contributing to the higher risk

Table 3 Risk ratios for ischemic placental disease and ischemic placental disease components in donor in vitro fertilization (IVF) and autologous IVF groups compared with non-IVF group

	Donor IVF ($n = 262$)	Autologous IVF ($n = 3501$)	Non-IVF ($n = 65321$)
Small for gestational age < 10th percentile			
Ischemic placental disease or IUFD	95 (36.3)	963 (27.5)	8773 (13.4)
Crude RR (95% CI)	2.7 (2.2–3.2)	2.0 (1.9–2.2)	1.0 (reference)
Adjusted RR (95% CI)[a]	2.9 (2.5–3.4)	2.0 (1.9–2.1)	1.0 (reference)
Preeclampsia	47 (17.9)	322 (9.2)	2354 (3.6)
Crude RR (95% CI)	5.0 (3.8–6.5)	2.6 (2.3–2.9)	1.0 (reference)
Adjusted RR (95% CI)[b]	3.8 (2.8–5.0)	2.2 (2.0–2.5)	1.0 (reference)
Placental abruption	12 (4.6)	111 (3.2)	843 (1.3)
Crude RR (95% CI)	3.5 (2.0–6.2)	2.5 (2.0–3.3)	1.0 (reference)
Adjusted RR (95% CI)[c]	3.8 (2.1–6.7)	2.5 (2.1–3.1)	1.0 (reference)
Small for gestational age	58 (22.1)	669 (19.1)	6207 (9.5)
Crude RR (95% CI)	2.3 (1.9–3.0)	2.0 (1.9–2.2)	1.0 (reference)
Adjusted RR (95% CI)[a]	2.7 (2.1–3.4)	2.0 (1.9–2.2)	1.0 (reference)
Small for gestational age < 3rd percentile			
Ischemic placental disease or IUFD	70 (26.7)	581 (16.6)	4452 (6.8)
Crude RR (95% CI)	3.9 (3.2–4.8)	2.4 (2.2–2.6)	1.0 (reference)
Adjusted RR (95% CI)[b]	3.4 (2.7–4.2)	2.3 (2.1–2.5)	1.0 (reference)
Small for gestational age	19 (7.3)	189 (5.4)	1433 (2.2)
Crude RR (95% CI)	3.3 (2.1–5.1)	2.5 (2.1–2.9)	1.0 (reference)
Adjusted RR (95% CI)[b]	3.4 (2.2–5.4)	2.5 (2.1–2.9)	1.0 (reference)

IVF, in vitro fertilization; *IUFD*, intrauterine fetal demise. Data presented as *n* (%) or risk ratio (RR) and 95% confidence interval (CI)

[a] Adjusted for age and parity

[b] Adjusted for age, parity, and marital status

[c] Adjusted for age

of IPD, because we found both an increased risk in donor IVF pregnancies, at risk for a heightened immune response, and autologous IVF pregnancies, where the immune response should resemble non-IVF pregnancies. Given both donor and autologous IVF pregnancies had a higher risk of IPD, it is likely that infertility, or the IVF treatment, plays a mechanistic role. While we did not evaluate the role of fresh or frozen embryo transfer in this study, we have previously found that pregnancies resulting from a frozen embryo transfer had a lower risk of IPD and SGA compared with pregnancies resulting from a fresh embryo transfer, among autologous IVF pregnancies in a subset of this cohort [27]. We were unable to evaluate whether donor IVF pregnancies or any IVF pregnancies identified via the birth certificate were the result of fresh or frozen embryo transfer. In addition, the higher risk in the donor IVF group compared with the autologous IVF group potentially indicates that a second mechanism, such as the heightened maternal immune response to the fetus, may also contribute.

This study has several limitations. Due to our reliance on electronic medical records, we did not have data on important potential confounders such as body mass index, prior IPD, infertility among the non-IVF group, other infertility treatments, and other medical history. We conducted a sensitivity analysis restricting our cohort to nulliparous women to evaluate the effect of IPD in a prior pregnancy and our results were similar. We were unable to evaluate the effect of obesity. We were also unable to evaluate the effect of partner or donor sperm in either the IVF or non-IVF groups. We were also not able to determine whether any of the IVF cycles were conducted using intracytoplasmic sperm injection. The outcomes of this study also vary in terms of severity and gestational age at diagnosis. Less severe types of preeclampsia and placental abruption may not affect clinical care, especially when they are diagnosed immediately prior to or at the time of delivery. This information was also not available.

The use of electronic medical records and billing data introduces potential for misclassification. With regard to exposure, it is likely that some women in our non-IVF group did undergo IVF. Furthermore, we did not assess whether women underwent another type of infertility treatment, such as intrauterine insemination. With regard to

Table 4 Risk ratios for ischemic placental disease and ischemic placental disease components in donor in vitro fertilization (IVF) group compared with autologous IVF group

	Donor IVF ($n = 262$)	Autologous IVF ($n = 3501$)
Small for gestational age < 10th percentile		
Ischemic placental disease or IUFD	95 (36.3)	963 (27.5)
Crude RR (95% CI)	1.3 (1.1–1.6)	1.0 (reference)
Adjusted RR (95% CI)*	1.5 (1.2–1.8)	1.0 (reference)
Preeclampsia	47 (17.9)	322 (9.2)
Crude RR (95% CI)	2.0 (1.5–2.6)	1.0 (reference)
Adjusted RR (95% CI)*	2.4 (1.8–3.3)	1.0 (reference)
Placental abruption	12 (4.6)	111 (3.2)
Crude RR (95% CI)	1.4 (0.8–2.6)	1.0 (reference)
Adjusted RR (95% CI)*	1.4 (0.8–2.7)	1.0 (reference)
Small for gestational age	58 (22.1)	669 (19.1)
Crude RR (95% CI)	1.2 (0.9–1.5)	1.0 (reference)
Adjusted RR (95% CI)*	1.2 (0.96–1.6)	1.0 (reference)
Small for gestational age < 3rd percentile		
Ischemic placental disease or IUFD	70 (26.7)	581 (16.6)
Crude RR (95% CI)	1.6 (1.3–2.0)	1.0 (reference)
Adjusted RR (95% CI)*	1.8 (1.4–2.3)	1.0 (reference)
Small for gestational age	19 (7.3)	189 (5.4)
Crude RR (95% CI)	1.3 (0.9–2.1)	1.0 (reference)
Adjusted RR (95% CI)*	1.4 (0.8–2.2)	1.0 (reference)

IVF, in vitro fertilization; *IUFD*, intrauterine fetal demise. Data presented as n (%) or risk ratio (RR) and 95% confidence interval (CI)

*Adjusted for age

outcome, due to unavailability of medical records, we were not able to confirm all of the ICD9 codes. The ICD9 codes had high positive predictive value (89.3% for preeclampsia and 89.7% for placental abruption); however, some women classified as having preeclampsia or placental abruption may not have been true cases. Conversely, we may have missed some cases of preeclampsia or placental abruption. We would anticipate the outcome misclassification to be non-differential with respect to exposure and to attenuate our results given that the medical management for these conditions would not differ by IVF procedure. The results of our probabilistic quantitative bias analysis are reassuring. There was no difference in the RR for the relationship between IVF and IPD or an IUFD related to placental insufficiency, likely due to the large non-IVF group. When we corrected for outcome misclassification, we found that our observed estimates are biased towards the null; thus, our inability to confirm all of the preeclampsia and placental abruption diagnoses is not likely to explain our results.

Another limitation is that we used singleton growth curves to calculate SGA for both singletons and multiples. Given multiples generally are smaller at all gestational ages; this could have led to an over-diagnosis of SGA in the multiples. Singleton growth curves are used in clinical practice at our institution for multiples. We were unable to assess Dopplers for SGA.

Our use of data from one institution may limit the generalizability of the results. However, the demographic characteristics of the IVF groups in our study are representative of IVF populations in other studies and the differences that we saw between the IVF and non-IVF groups were expected. In addition, the overall incidence of preeclampsia, placental abruption, and SGA in our population was similar to what has been reported previously.

Finally, we were only able to assess the association between IVF and IPD among pregnancies that were 20 weeks of gestation or greater. We do not know about the risk of IPD among pregnancies that did not survive to 20 weeks. In order for this to explain the results from this study, the risk of IPD after 20 weeks of gestation would need to be greater among pregnancies lost in the non-IVF group. It is more likely that the risk of IPD would be greater among pregnancies lost in the IVF groups, biasing our estimate towards the null.

Strengths of the study include the large sample size and the use of both IVF and obstetrical records. This allowed us to examine the individual components of IPD, adjust for several confounders, and conduct multiple sensitivity analyses. In addition, exposure, outcome, and covariate data were recorded prospectively in medical records and there was no need to rely on physician recall or maternal report. The use of a composite outcome comprised of four individual pregnancy complications that share a common set of risk factors and potential common pathophysiology can help clarify underlying causal mechanisms and makes our study more novel. Finally, we have chosen to compare donor IVF and autologous IVF pregnancies to non-IVF pregnancies, as well as comparing donor IVF and autologous IVF pregnancies which contributes to our understanding of the mechanisms.

Conclusion

The present study found that pregnancies conceived via donor IVF or autologous IVF had a higher risk of IPD than non-IVF pregnancies. This was particularly the case for preeclampsia and SGA when restricted to < 3rd percentile. Associations were consistently stronger for donor IVF than autologous IVF. Our results suggest that women undergoing IVF should be counseled about these risks and increased maternal/fetal surveillance may be considered. Future research into the pathophysiology underlying these differences and the study of

possible means to reduce these risks in autologous and particularly donor IVF pregnancies are warranted.

Acknowledgments We would like to acknowledge Laura Dodge and JoAnn Jordan for their assistance with obtaining data for this study. We would also like to acknowledge Stacey Missmer and Olga Basso for their review of this study.

Study funding AMM was supported by NIH T32 HD052458—Boston University Reproductive, Perinatal and Pediatric Epidemiology Training Program.

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