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ORIGINAL ARTICLE

Multifoetal gestations mediate the effect of in vitro fertilisation (IVF) on ischaemic placental disease in autologous oocyte IVF more than donor oocyte IVF

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Abstract

Background: Ischaemic placental disease (IPD) affects 16%–23% of pregnancies in the United States. In vitro fertilisation (IVF) is a risk factor for IPD, and the magnitude of increase in risk differs for individuals using donor oocytes (donor IVF) versus their own oocytes (autologous IVF). In addition, multifoetal gestations, which are more common in IVF than non-IVF pregnancies, also are a risk factor for IPD.

Objective: To quantify the contribution of multifoetal gestations to the association between IVF and IPD.

Methods: We conducted a retrospective cohort study at a tertiary hospital from 1 January, 2000 to 1 August 2018 using electronic medical records and state vital statistics data. IPD was defined as preeclampsia, placental abruption, small for gestational age (SGA) birth or an intrauterine foetal demise due to placental insufficiency. We used mediation analysis to decompose the total effect of IVF on IPD into a natural direct effect and an indirect effect through multifoetal gestations. We repeated the analyses separately for donor and autologous IVF. All models were adjusted for maternal age, race, parity, insurance, year of delivery and account for multiple pregnancies per person.

Results: We identified 86,514 deliveries, of which 281 resulted from donor IVF and 4173 resulted from autologous IVF. IVF pregnancies had 1.99 (95% CI 1.88, 2.10) times the risk of IPD compared to non-IVF pregnancies, and 75.5% of this increased risk was mediated by multifoetal gestations. Autologous IVF pregnancies had 1.95 (95% CI 1.84, 2.07) times the risk of IPD compared to non-IVF pregnancies, and the per cent mediated was 78.8%. Donor IVF pregnancies had 2.50 (95% CI 2.09, 2.92) times the risk of IPD, but the per cent mediated was 37.5%.

Conclusion: The majority of the association between autologous IVF and IPD was mediated through multifoetal gestations; however, this was not the case for donor IVF pregnancies.

KEYWORDS
autologous IVF, donor IVF, in vitro fertilisation, ischaemic placental disease, mediation analysis, multifoetal gestations

1 | BACKGROUND

Ischaemic placental disease (IPD) affects 16%–23% of pregnancies in the United States. In vitro fertilisation (IVF) is a risk factor for IPD, with individuals using donor oocytes (donor IVF) at a higher risk of IPD compared to individuals using their own oocytes (autologous IVF).[1] There are several proposed mechanisms for this increased risk, including the increased likelihood of multifoetal gestations among IVF pregnancies. In a previous study, we found that 35.3% of IVF pregnancies were multifoetal gestations compared to only 2.2% of non-IVF pregnancies.[1] Multifoetal gestations are at greater risk for IPD, independent of mode of conception.[2,3] It is possible that some of the increased risk of IPD in IVF pregnancies is due to the higher incidence of multifoetal gestations in IVF than non-IVF pregnancies.[4] Restricting our prior cohort to singleton gestations, the risk of IPD in IVF compared to non-IVF pregnancies was attenuated.[1] However, adjusting for or excluding multifoetal gestations, a variable on the causal pathway between our exposure and outcome, may lead to bias.[4,5]

Mediation analysis is a statistical approach that can be used in situations where the exposure (IVF) causes the mediator (multifoetal gestations), which then causes the outcome (IPD).[4,6,7] It allows us to explore and quantify two different causal mechanisms to explain the observed relationship: the direct effect of IVF on IPD, and the indirect effect of IVF on IPD, or the relationship that is mediated by multifoetal gestations.[6,7] Our objective was to determine the role of multifoetal gestations in the association between IVF and IPD. Furthermore, we aimed to assess the role of multifoetal gestations separately for donor IVF and autologous IVF pregnancies.

Synopsis

Study question

What is the contribution of multifoetal gestations to the association between in vitro fertilisation (IVF) and ischaemic placental disease (IPD)?

What's already known

IPD affects 16%–23% of pregnancies in the United States. IVF is a risk factor for IPD, and the magnitude of the increase in risk differs for individuals using donor IVF versus their own oocytes (autologous IVF). In addition, multifoetal gestations, which are more common in IVF than non-IVF pregnancies, also are a risk factor for IPD.

What this study adds

The majority of the association between autologous IVF and IPD was mediated through multifoetal gestations; however, this was not the case for donor oocytes (donor IVF) pregnancies.

2 | METHODS

2.1 | Cohort selection

This was a retrospective cohort study of deliveries at a tertiary care hospital in Boston, MA, from 1 January 2000 to 1 August 2018. Deliveries were linked to IVF cycles performed by the hospital's reproductive endocrinology and infertility division. The methods for this cohort have been previously described.[1] The initial cohort, which included deliveries through 1 June 2015, was expanded through 1 August 2018 using similar methods and incorporating ICD10 codes. An internal validation of ICD10 codes was conducted for all pregnancies through 31 December 2016 using the same methodology as described previously.[1] Deliveries also were linked to data from the Massachusetts Department of Public Health (MA DPH) vital statistics from 1 January 2000 to 1 June 2015. (Table S1).

2.2 | Exposure

IVF pregnancies were identified using medical records from the reproductive endocrinology and infertility division and birth certificate data. Of note, the data available from the birth certificate are self-reported by the mother at the time of delivery.

2.3 | Outcomes

Our primary outcome was IPD, defined as preeclampsia, placental abruption or small for gestational age (SGA), or an intrauterine foetal demise (IUFD) due to placental insufficiency. Although IUFD is not traditionally included in the definition of IPD, IUFDs where the known cause was placental insufficiency were included due to a similar biological mechanism and concerns that pregnancies with an IUFD due to placental insufficiency would likely have developed preeclampsia, placental abruption or SGA had they survived. Preeclampsia, placental abruption and IUFD were identified using ICD9 and ICD10 codes. All IUFDs were reviewed in the medical record for gestational age and cause of IUFD. An IUFD was attributed to placental insufficiency if this was a cause noted in the pathology, autopsy or clinical consultation notes. SGA was defined as birthweight <10th percentile adjusted for gestational age and infant sex, using a US population as the norm.[8] In order to isolate infants who were more likely to be pathologically small, we conducted a secondary analysis using <3rd percentile as the definition of SGA.[9,10] All outcomes were assessed at the level of the pregnancy. Therefore, for multifoetal gestations, if one of the infants had SGA or/and IUFD, then the pregnancy was considered to be affected.

2.4 | Statistical analysis

Data are presented as mean ± standard deviation or *n* (%). We calculated risk ratios and 95% confidence intervals using generalised estimating equations with an unstructured correlation matrix to account for repeated pregnancies for the same person. Confounders were chosen with the aid of directed acyclic graphs.[11,12] Models were adjusted for maternal age, race, parity

and year of delivery. Year of delivery was added to account for temporal changes over the 18-year study period. Race we included in the model as a marker of socioeconomic position and structural and interpersonal racism.

We then used mediation analysis to decompose the total effect of IVF versus non-IVF pregnancies on IPD into a direct effect and an indirect effect through multifoetal gestations[6] (Figure 1). We fit two regression models. The first was a log-binomial regression to estimate the joint effect of IVF and multifoetal gestations on IPD. We included an interaction term to allow the risk ratios for the effect of multifoetal gestations to differ depending on whether IVF was used. The second model was a logistic regression to estimate predicted probabilities of a multifoetal gestation after IVF, conditional on covariates. Each included covariates to control for exposure–outcome (U_1 in Figure 1), exposure–mediator (U_2 in Figure 1) and mediator–outcome confounding (U_3 in Figure 1): maternal age, race, parity, insurance and year of delivery. Coefficients from these models were combined to estimate the direct and indirect effects on the risk ratio scale. More specifically, we estimated the natural direct effect, which quantifies the effect of IVF on IPD independent of multifoetal gestations.[6,7] We estimated the proportion mediated on the risk difference scale.[4] We used bootstrapping with 2000 replications to estimate 95% confidence intervals for each effect, accounting for multiple pregnancies from the same person.

We repeated the analyses separately for donor and autologous IVF pregnancies, using non-IVF pregnancies as the reference for all analyses. For each of these analyses, we used the same data structure as for the overall IVF and IPD analysis, substituting either autologous IVF or donor IVF in place of all IVF in Figure 1. The same confounders were included. All analyses were conducted in SAS 9.4 (SAS Institute Inc.).

2.5 | Missing data

Complete case analysis was conducted given that none of the covariates had more than 5% missing data. Observations with missing data are listed in Table 1, and include gravidity (missing for 0.05%) and parity (missing for 0.03%). Unknown race was included as a category. The complete case analysis included 99% of all records.

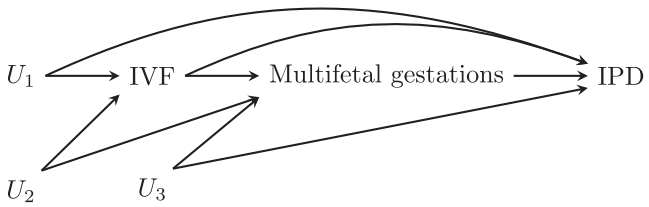

FIGURE 1 Directed acyclic graph of the relationship between in vitro fertilisation (IVF) and ischaemic placental disease (IPD) mediated by multifoetal gestations. U_1 represents exposure–outcome confounders; U_2 represents exposure–mediator confounders; U_3 represents mediator–outcome confounders

2.6 | Sensitivity analyses

First, we restricted deliveries to those after 2013. This was done to account for changes in IVF technology, notably the switch to vitrification for freezing embryos, which we adopted widely in 2013.[13] Next, we assessed possible unmeasured confounding. Because we did not have data on obstetric history, a possible confounder of the exposure–outcome relationship, we first restricted the sample to nulliparous individuals. In addition, since there were two covariates of interest in the MA DPH data, smoking and pre-gestational diabetes, which were not available for deliveries beyond 1 June 2015, we conducted a sensitivity analysis using data from 1 January 2000 to 1 June 2015 to adjust for those additional covariates. Finally, we computed E-values, both for the total exposure–outcome effect and specifically considering possible unmeasured mediator–outcome confounding.[14,15]

2.7 | Ethics approval

The institutional review boards at Beth Israel Deaconess Medical Center and the MA DPH approved this study.

3 | RESULTS

3.1 | Study population

We identified 86,514 deliveries that met our inclusion criteria. Of these, 281 resulted from donor IVF and 4173 resulted from autologous IVF. Individuals in the IVF group were more likely to be older, White, primigravid and nulliparous compared to the non-IVF group. They also were more likely to have private insurance. In the IVF group, 1278 (28.7%) deliveries were multifoetal gestations, while 1816 (2.2%) of the non-IVF group were multifoetal gestations. Among the donor IVF group, 34.9% (98/281) were multifoetal gestations and among the autologous IVF group, 28.3% (1180/4173) were multifoetal gestations (Table 1). IPD and the individual components are also presented. Of note, there were a total of 15 (0.3%) IUFDs in the IVF group and 364 (0.4%) in the non-IVF group, although not all were attributed to placental insufficiency. Information on zygosity was not available; however, 638 (50.0%) of IVF pregnancies were multiple sex sets, and 577 (31.8%) of non-IVF pregnancies were multiple sex sets. Multiple sex sets were similar in the donor and autologous group (50.0% in each).

3.2 | Effect of multifoetal gestation on IPD

Pregnancies with multifoetal gestations were at a higher risk of IPD and each of its components compared to pregnancies with singleton gestations. Multifoetal gestation pregnancies had 3.87 (95% CI 3.73, 4.03) times the adjusted risk of IPD compared to pregnancies with singleton gestations (adjusted for maternal age, parity, race and year

TABLE 1 Baseline characteristics of deliveries from 1 January 2000 to 1 August 2018 IVF and non-IVF cohorts and among multifoetal gestations ($n = 85{,}799$)

	IVF			Non-IVF		
	All deliveries $n = 4454$	**Singleton gestations** $n = 3176$	**Multifoetal gestations** $n = 1278$	**All deliveries** $n = 81345$	**Singleton gestations** $n = 79529$	**Multifoetal gestations** $n = 1816$
Baseline demographics						
Maternal age (years)	36.2 ± 4.7	36.5 ± 4.7	35.4 ± 4.6	31.7 ± 4.9	31.7 ± 4.9	32.2 ± 5.1
Race						
Non-Hispanic White	3539 (79.5)	2485 (78.2)	1054 (82.5)	46722 (57.4)	45539 (57.3)	1183 (65.1)
Non-Hispanic Black	175 (3.9)	131 (3.8)	54 (4.2)	9696 (11.9)	9503 (12.0)	193 (10.6)
Asian	346 (7.8)	270 (8.5)	76 (5.9)	12297 (15.1)	12156 (15.3)	141 (7.8)
Hispanic	86 (1.9)	63 (2.0)	23 (1.8)	4800 (5.9)	4692 (5.9)	108 (5.9)
Other	217 (4.9)	156 (4.9)	61 (4.8)	4679 (5.8)	4568 (5.7)	111 (6.1)
Unknown	91 (2.0)	81 (2.6)	10 (0.8)	3151 (3.9)	3071 (3.9)	80 (4.4)
Gravidity						
1	2503 (56.2)	1746 (55.0)	757 (59.2)	30069 (37.0)	29374 (36.9)	695 (38.3)
2	1007 (22.6)	738 (23.2)	269 (21.0)	25954 (31.9)	25435 (32.0)	519 (28.6)
3+	942 (21.1)	690 (21.7)	252 (19.7)	25281 (31.1)	24679 (31.0)	602 (33.1)
Missing	2 (0.04)	2 (0.1)	0 (0.0)	41 (0.1)	41 (0.1)	0 (0.0)
Parity						
0	2933 (65.9)	2036 (64.1)	897 (70.2)	38274 (47.1)	37341 (47.0)	933 (51.4)
1	1267 (28.4)	948 (29.8)	319 (25.0)	29199 (35.9)	28601 (36.0)	598 (32.9)
2	207 (4.6)	155 (4.9)	52 (4.1)	10088 (12.4)	9894 (12.4)	194 (10.7)
3+	45 (1.0)	35 (1.1)	10 (0.8)	3756 (4.6)	3665 (4.6)	91 (5.0)
Missing	2 (0.02)	2 (0.1)	0 (0.0)	28 (0.03)	28 (0.04)	0 (0.0)
Insurance status						
Private/other	4384 (98.4)	3123 (98.3)	1261 (98.7)	68703 (83.7)	66512 (83.6)	1561 (86.0)
Public	70 (1.6)	53 (1.7)	17 (1.3)	13272 (16.3)	13017 (16.4)	255 (14.0)
Oocyte source						
Donor	281 (6.3)	183 (5.8)	98 (7.7)	-	-	-
Autologous	4173 (93.7)	2993 (94.2)	1180 (92.3)	-	-	-
Outcomes						
Small for gestational age <10th percentile						
Ischaemic placental disease or IUFD	1219 (27.4)	535 (16.8)	684 (53.5)	11655 (14.3)	10733 (13.5)	922 (50.8)

TABLE 1 (Continued)

	IVF			Non-IVF		
	All deliveries $n = 4454$	Singleton gestations $n = 3176$	Multifoetal gestations $n = 1278$	All deliveries $n = 81345$	Singleton gestations $n = 79529$	Multifoetal gestations $n = 1816$
Preeclampsia	452 (10.1)	207 (6.5)	245 (19.2)	3342 (4.1)	3068 (3.9)	274 (15.1)
Placental abruption	138 (3.1)	83 (2.6)	55 (4.3)	1235 (1.5)	1203 (1.5)	32 (1.8)
IUFD due to placental insufficiency	5 (0.1)	3 (0.1)	2 (0.2)	183 (0.2)	177 (0.2)	6 (0.3)
Small for gestational age	813 (18.3)	314 (9.9)	499 (39.0)	7959 (9.8)	7219 (9.1)	740 (40.7)
Small for gestational age <3rd percentile						
Ischaemic placental disease or IUFD	765 (17.2)	349 (11.0)	416 (32.6)	6135 (7.5)	5638 (7.1)	497 (27.4)
Small for gestational age	229 (5.1)	75 (2.4)	154 (12.1)	1827 (2.2)	1601 (2.0)	226 (12.4)

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

Abbreviations: IUFD, Intrauterine foetal demise (due to placental insufficiency); IVF, in vitro fertilisation.

of delivery). In the IVF group, pregnancies with multifoetal gestations had 3.25 (95% CI 2.96, 3.57) times the adjusted risk of IPD, and in the non-IVF group, pregnancies with multifoetal gestations had 3.81 (95% CI 3.62, 4.00) times the adjusted risk of IPD compared to singleton gestations. There was a similar pattern of increased risk for each of the individual components of IPD including both definitions of SGA. (Table 2). IUFDs were not assessed individually as a component due to small sample size.

3.3 | Effect of IVF on IPD

Overall, IVF pregnancies had 1.99 (95% CI 1.88, 2.10) times the risk of IPD compared to non-IVF pregnancies, adjusted for maternal age, parity, race and year of delivery, and 75.5% of this increased risk was mediated by multifoetal gestations. Autologous IVF pregnancies had 1.95 (95% CI 1.4, 2.07) times the adjusted risk of IPD compared to non-IVF pregnancies, and the proportion mediated by multifoetal gestations was 78.8%. Donor IVF pregnancies had 2.50 (95% CI 2.09, 2.92) times the adjusted risk of IPD but the per cent mediated was 37.5%. Among the components of IPD, similar patterns of results were noted. The per cent mediated of the association between autologous IVF and the components of IPD was 42.4–86.7%, but the per cent mediated by multifoetal gestations in the associations between donor IVF and the components of IPD was 24.6%–60.1%. (Table 3).

3.4 | Sensitivity analyses

In sensitivity analyses, a similar pattern of results was seen among nulliparous individuals (Table S2). IVF pregnancies had 1.78 (95% CI 1.66, 1.91) times the risk of IPD compared to non-IVF pregnancies. The per cent mediated by pregnancies with multifoetal gestations in the association between autologous IVF and IPD and donor IVF and IPD was 84.5% and 38.8%, respectively, among nulliparous individuals. A similar pattern was noted when restricting the cohort to deliveries after 2013 (Table S3). IVF pregnancies had 1.57 (95% CI 1.41, 1.73) times the risk of IPD compared to non-IVF pregnancies. The per cent mediated by pregnancies with multifoetal gestations in the association between autologous IVF and IPD and donor IVF and IPD was 68.0% and 15.6%, respectively, among all pregnancies in this more recent cohort. In the sensitivity analysis for years in which MA DPH data was available, the mediation models did not converge due to low numbers of smoking and pre-gestational diabetes prior to pregnancy. However, we did fit regression models for the total effect and there was no difference when adjusting for smoking and pre-gestational diabetes. E-values (Table S4) further demonstrated that only very strong unmeasured confounders could explain away the total effects; for example, a confounder (or set of confounders) would have to increase risk of IPD and differ between IVF and non-IVF pregnancies by a factor of 3.4, independently of the measured confounders, to account for the overall effect. E-values for the indirect effects were (by definition) smaller, meaning that weaker

TABLE 2 Risk of ischaemic placental disease and ischaemic placental disease components in multifoetal gestations compared to singleton gestations among all deliveries, and by mode of conception ($n = 85,799$)

		Risk ratio[a] (95% confidence interval)		
		All deliveries	IVF	Non-IVF
Small for gestational age <10th percentile				
Ischaemic placental disease or IUFD				
Multifoetal gestations	1606 (51.9)	3.87 (3.73, 4.03)	3.25 (2.96, 3.57)	3.81 (3.62, 4.00)
Singleton gestations	11268 (13.6)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Preeclampsia				
Multifoetal gestations	519 (16.8)	4.11 (3.77, 4.48)	3.21 (2.70, 3.83)	3.80 (3.39, 4.26)
Singleton gestations	3275 (4.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Placental abruption				
Multifoetal gestations	87 (2.8)	1.90 (1.53, 2.35)	1.63 (1.16, 2.28)	1.18 (0.83, 1.67)
Singleton gestations	1286 (1.6)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Small for gestational age				
Multifoetal gestations	1239 (40.0)	4.55 (4.33, 4.78)	3.94 (3.46, 4.48)	4.62 (4.35, 4.91)
Singleton gestations	7533 (9.1)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Small for gestational age <3rd percentile				
Ischaemic placental disease or IUFD				
Multifoetal gestations	913 (29.5)	4.08 (3.84, 4.33)	3.12 (2.74, 3.54)	3.84 (3.55, 4.16)
Singleton gestations	5987 (7.2)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Small for gestational age				
Multifoetal gestations	380 (12.3)	6.27 (5.64, 6.98)	5.13 (3.91, 6.72)	6.37 (5.58, 7.26)
Singleton gestations	1676 (2.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

Note: Data presented as *n* (%) or risk ratio (95% confidence interval).

Abbreviations: IUFD: intrauterine foetal demise (due to placental insufficiency); IVF: In vitro fertilisation.

[a]Risk ratios adjusted for maternal age, parity, race and year of delivery.

confounding could be compatible with truly null indirect effects (which would imply that the totality of a given effect was direct). For example, the E-value for the indirect effect of overall IVF on IPD mediated through multifoetal gestations was 2.6.

4 | COMMENT

4.1 | Principal findings

Consistent with prior literature, we found an increased risk of IPD and its components in autologous and donor IVF pregnancies when compared to non-IVF pregnancies.[1,14,16,17] For autologous IVF, the majority of IPD was mediated through multifoetal gestations, which was consistent with a prior study.[4] We showed that in donor IVF, 37.5% of the relationship was mediated through multifoetal gestations, meaning that approximately 60% of the relationship between donor IVF and IPD was not explained by the increased incidence of pregnancies with multifoetal gestations. This also was true for components of IPD, including preeclampsia and placental abruption. This difference suggests different mechanisms for the increased risk of IPD in donor and autologous pregnancies.

4.2 | Strengths of the study

The strengths of this study include a large sample size, and the ability to examine donor and autologous IVF pregnancies separately. In addition, our use of a composite outcome allowed us to assess a group of biologically related conditions, as well as the components of IPD separately.

4.3 | Limitations of the data

This study has several limitations. First, we were unable to obtain some of the covariate data that may be important to this question, particularly body mass index, medical history and comorbidities. We were also not able to determine the number of gestations at the start of the pregnancy to assess for whether there were early losses in our singleton pregnancies. This would lead to residual confounding as we may not have met the unmeasured confounding assumptions of mediation analysis, which include no unmeasured confounders of the exposure–outcome relationship, no unmeasured confounders of the exposure–mediator relationship, no unmeasured confounders of the mediator–outcome relationship and no mediator–outcome

TABLE 3 Risk of ischaemic placental disease and ischaemic placental disease components overall (total effect), independent of multifoetal gestations (natural direct effect), mediated through multifoetal gestations (indirect) and the per cent of the risk of ischaemic placental disease mediated through multifoetal gestations (n = 85,799)

	Total effect RR (95% CI)	Natural direct effect RR (95% CI)	Indirect effect RR (95% CI)	Percent mediated
Small for gestational age <10th percentile				
Ischaemic placental disease or IUFD				
All IVF	1.99 (1.88, 2.10)	1.24 (1.15, 1.34)	1.60 (1.52, 1.69)	75.5
Autologous IVF	1.95 (1.84, 2.07)	1.20 (1.10, 1.29)	1.63 (1.54, 1.72)	78.8
Donor IVF	2.50 (2.09, 2.92)	1.93 (1.49, 2.38)	1.29 (1.14, 1.51)	37.5
Preeclampsia				
All IVF	2.20 (1.98, 2.43)	1.40 (1.21, 1.59)	1.58 (1.45, 1.73)	67.2
Autologous IVF	2.11 (1.89, 2.35)	1.30 (1.12, 1.48)	1.62 (1.48, 1.79)	73.0
Donor IVF	3.37 (2.48, 4.33)	2.78 (1.99, 3.76)	1.21 (1.02, 1.53)	24.6
Placental abruption				
All IVF	2.22 (1.82, 2.66)	1.81 (1.43, 2.24)	1.22 (1.08, 1.42)	33.3
Autologous IVF	2.19 (1.79, 2.61)	1.68 (1.32, 2.08)	1.30 (1.14, 1.52)	42.4
Donor IVF	2.90 (1.43, 4.71)	3.87 (1.84, 6.39)	0.75 (0.65, 0.93)	-
Small for gestational age				
All IVF	2.05 (1.91, 2.20)	1.16 (1.04, 1.28)	1.77 (1.65, 1.91)	85.1
Autologous IVF	2.02 (1.88, 2.18)	1.14 (1.02, 1.26)	1.78 (1.66, 1.93)	86.7
Donor IVF	2.38 (1.83, 2.92)	1.55 (1.04, 2.13)	1.54 (1.24, 2.08)	60.1
Small for gestational age <3rd percentile				
Ischaemic placental disease or IUFD				
All IVF	2.21 (2.05, 2.38)	1.41 (1.28, 1.55)	1.57 (1.47, 1.68)	66.2
Autologous IVF	2.15 (1.99, 2.32)	1.35 (1.20, 1.49)	1.59 (1.49, 1.72)	69.7
Donor IVF	3.06 (2.46, 3.70)	2.40 (1.75, 3.06)	1.28 (1.11, 1.55)	32.3
Small for gestational age				
All IVF	2.45 (2.11, 2.83)	1.19 (0.96, 1.47)	2.05 (1.76, 2.40)	86.6
Autologous IVF	2.38 (2.04, 2.76)	1.21 (0.96, 1.47)	1.96 (1.69, 2.32)	84.6
Donor IVF	3.21 (1.89, 4.58)	0.95 (0.22, 1.85)	3.37 (1.88, 12.11)	-

Note: Data presented as risk ratio (RR) and 95% confidence interval (CI) or per cent. All models adjusted for maternal age, parity, race and year of delivery.

Unable to present percent mediated due to opposing natural direct and indirect effects

Abbreviations: IUFD, intrauterine foetal demise; IVF, In vitro fertilisation.

confounder that is affected by exposure.[7] However, among nulliparous individuals, who cannot have a history of IPD, our results were similar, and total effects were similar in analyses in which we accounted for smoking and pre-gestational diabetes. Other unmeasured confounders are unlikely to have associations above and beyond these factors that would be as large as the E-values for the

total effects. In addition, while E-values for indirect effects are smaller, we know of fewer possible confounders of the mediator; it is unlikely that factors beyond those we accounted for increased or decreased the risk of multifoetal gestations by meaningful amount.

Second, due to our methodology in linking IVF cycles to deliveries,[1] it is likely that there are IVF pregnancies in our non-IVF group. If so, we would expect that the overall association between IVF and IPD would be biased towards the null, as seen in prior work,[1] and that our natural direct effect also likely would be biased towards the null.[18] It is not immediately clear how this would affect the indirect effect or the per cent mediated. Third, there likely is some outcome misclassification, such that we missed deliveries with IPD or incorrectly diagnosed deliveries with IPD. The positive predictive value of the ICD codes used to identify outcomes was approximately 90% for both preeclampsia and placental abruption[1]; thus, the misclassification likely is minimal. It is also likely that we are missing IPD diagnoses. However, given the severity of the diagnoses and need for obstetrical intervention, we believe this misclassification is also likely minimal. We believe the outcome misclassification would be non-differential, which would bias our natural direct and indirect effects towards the null and not bias our per cent mediated.[18] Additional outcome misclassification may have occurred among the IUFDs when calculating SGA. SGA is based on birthweight, which is difficult to determine in IUFDs, particularly if there has been any maceration prior to delivery. However, we do not believe this would substantially affect our results since the number of IUFDs in this cohort is very small and we believe the misclassification would be non-differential. Our use of singleton growth curves for multifoetal gestations in the calculation of SGA could also lead to misclassification, since infants born from multifoetal gestations are expected to be smaller. However, singleton growth curves are used clinically, and we believe this misclassification would be non-differential.

4.4 | Interpretation

The differences in causal pathways for IPD in donor and autologous IVF are critical in both understanding the underlying biology and identifying targets for future research. Some of these differences may be explained by the difference in immunogenicity of the pregnancy. The increased risk of IPD in IVF pregnancies has been hypothesised to be related to the maternal immune response.[16,19-21] In any pregnancy, the maternal immune system can develop an inflammatory response against'foreign' foetal or placental tissues that have partial paternal genetic origin. An overactive maternal immune response may lead to insufficient placentation and IPD.[22] In pregnancies with multifoetal gestations, the amount of paternal antigen increases with each additional foetus. Pregnancies conceived with donor oocyte IVF contain a greater burden of foreign genetic material from both gametes than autologous oocyte IVF and may be at higher risk of a heightened immune response regardless of multifoetal pregnancy status. Consistent phenotyping of IPD based on common mediating factors will foster discovery of shared pathological mechanisms and therapeutic strategies.[23] Future research examining the biology of IPD in donor IVF pregnancies will be critical to understanding this potentially different mechanism of IPD. Additionally, further research should explore the effects of changes in the number of foetuses over pregnancy and discordant outcomes for foetuses. More information regarding the IVF process, role of infertility and zygosity would also be important to incorporate.

5 | CONCLUSIONS

While much of the relationship between IVF and IPD can be explained by the increase in multifoetal gestations, special attention should be paid to donor IVF pregnancies, where the increased risk may be due to a second biological mechanism, which needs further study. The association between IVF and IPD is complex and future work is needed to explore the factors contributing to this relationship.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

AMM: Conceived of the study design, completed the data analysis, wrote the manuscript. LHS: Significant contribution to conception of study design, analysis, and interpretation of the data, critically revised manuscript, approved final version. TLT: Significant contribution to interpretation of data, critically revised manuscript, approved final version. AYC: Significant contribution to interpretation of data, critically revised manuscript, approved final version. MRH: Significant contribution to conception of study design, analysis, and interpretation of the data, critically revised manuscript, approved final version.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Modest AM, Johnson KM, Karumanchi SA, et al. Risk of ischemic placental disease is increased following in vitro fertilization with oocyte donation: a retrospective cohort study. *J Assist Reprod Genet*. 2019;36(9):1917-1926. doi:10.1007/s10815-019-01545-3
2. Parker SE, Werler MM. Epidemiology of ischemic placental disease: a focus on preterm gestations. *Semin Perinatol*. 2014;38(3):133-138. doi:10.1053/j.semperi.2014.03.004

3. Watanabe N, Fujiwara T, Suzuki T, et al. Is in vitro fertilization associated with preeclampsia? A propensity score matched study. *BMC Pregnancy Childbirth*. 2014;14(1):69. doi:10.1186/1471-2393-14-69
4. Oberg AS, VanderWeele TJ, Almqvist C, Hernandez-Diaz S. Pregnancy complications following fertility treatment-disentangling the role of multiple gestation. *Int J Epidemiol*. 2018;47(4):1333-1342. doi:10.1093/ije/dyy103
5. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology*. 2009;20(4):488-495. doi:10.1097/EDE.0b013e3181a819a1
6. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. 2013;18(2):137-150. doi:10.1037/a0031034
7. Farland LV, Correia KFB, Dodge LE, et al. The importance of mediation in reproductive health studies. *Hum Reprod*. 2020;35(6):1262-1266. doi:10.1093/humrep/deaa064
8. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr*. 2003;3(1):6. doi:10.1186/1471-2431-3-6
9. Spiel M, Salahuddin S, Pernicone E, et al. Placental soluble fms-like tyrosine kinase expression in small for gestational age infants and risk for adverse outcomes. *Placenta*. 2017;52:10-16. doi:10.1016/j.placenta.2017.02.011
10. Ananth CV, Smulian JC, Vintzileos AM. Ischemic placental disease: maternal versus fetal clinical presentations by gestational age. *J Matern Fetal Neonatal Med*. 2010;23(8):887-893. doi:10.3109/14767050903334885
11. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48. doi:10.1097/00001648-199901000-00008
12. Ananth CV, Schisterman EF. Confounding, causality, and confusion: the role of intermediate variables in interpreting observational studies in obstetrics. *Am J Obstet Gynecol*. 2017;217(2):167-175. doi:10.1016/j.ajog.2017.04.016
13. Johnson KM, Hacker MR, Resetkova N, O'Brien B, Modest AM. Risk of ischemic placental disease in fresh and frozen embryo transfer cycles. *Fertil Steril*. 2019;111(4):714-721. doi:10.1016/j.fertnstert.2018.11.043
14. Van Der Weele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607
15. Smith LH, Vanderweele TJ. Mediational E-values: approximate sensitivity analysis for unmeasured mediator-outcome confounding. *Epidemiology*. 2019;30(6):835-837. doi:10.1097/EDE.0000000000001064
16. Klatsky PC, Delaney SS, Caughey AB, Tran ND, Schattman GL, Rosenwaks Z. The role of embryonic origin in preeclampsia: a comparison of autologous in vitro fertilization and ovum donor pregnancies. *Obstet Gynecol*. 2010;116(6):1387-1392. doi:10.1097/AOG.0b013e3181fb8e59
17. Elenis E, Sydsjö G, Skalkidou A, Lampic C, Svanberg AS. Neonatal outcomes in pregnancies resulting from oocyte donation: a cohort study in Sweden. *BMC Pediatr*. 2016;16(1):170. doi:10.1186/s12887-016-0708-5
18. Jiang Z, Vanderweele T. Causal mediation analysis in the presence of a misclassified binary exposure. *Epidemiol Method*. 2019;8(1):20160006. doi:10.1515/em-2016-0006
19. Jeve Y, Potdar N, Opoku A, Khare M. Donor oocyte conception and pregnancy complications: a systematic review and meta-analysis. *BJOG an Int J Obstet Gynaecol*. 2016;123(9):1471-1480. doi:10.1111/1471-0528.13910
20. Martínez-Varea A, Pellicer B, Perales-Marín A, Pellicer A. Relationship between maternal immunological response during pregnancy and onset of preeclampsia. *J Immunol Res*. 2014;2014:1-15. doi:10.1155/2014/210241
21. van der Hoorn M-LP, van Egmond A, Swings GMJS, et al. Differential immunoregulation in successful oocyte donation pregnancies compared with naturally conceived pregnancies. *J Reprod Immunol*. 2014;101–102:96-103. doi:10.1016/j.jri.2013.08.002
22. Collier AY, Smith LA, Karumanchi SA. Review of the immune mechanisms of preeclampsia and the potential of immune modulating therapy. *Hum Immunol*. 2021;82(5):362-370. doi:10.1016/j.humimm.2021.01.004
23. Maric-Bilkan C, Abrahams VM, Arteaga SS, et al. Research recommendations from the national institutes of health workshop on predicting, preventing, and treating preeclampsia. *Hypertension*. 2019;73(4):757-766. doi:10.1161/HYPERTENSIONAHA.118.11644

SUPPORTING INFORMATION

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