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Maternal factors and the risk of birth defects after IVF and ICSI: a whole of population cohort study

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Objective To assess the contribution of maternal factors to major birth defects after *in vitro* fertilisation (IVF), intracytoplasmic sperm injection (ICSI), and natural conception.

Design Retrospective cohort study in South Australia for the period January 1986 to December 2002.

Setting A whole of population study.

Population A census of all IVF and ICSI linked to registries for births, pregnancy terminations, and birth defects (diagnosed before a child's fifth birthday).

Methods Odds ratios (ORs) for birth defects were calculated among IVF, ICSI, and natural conceptions for maternal age, parity, pre-pregnancy BMI, smoking, pre-existing diseases, and conditions in pregnancy, with adjustment for confounding factors.

Main outcome measures Birth defects classified by International Classification of Diseases (ninth revision) and British Paediatric Association (ICD9-BPA) codes.

Results There were 2211 IVF, 1399 ICSI, and 301 060 naturally conceived births. The unadjusted prevalence of any birth defect was 7.1, 9.9, and 5.7% in the IVF, ICSI, and natural conception groups, respectively. As expected, the risk of birth defects increased with maternal age among the natural conceptions. In contrast, for IVF and ICSI combined, relative to natural conceptions, births to women aged ≤29 years had a higher risk (adjusted odds ratio, aOR 1.42; 95% confidence interval, 95% CI 1.04–1.94), births to women aged 35–39 years had no difference in risk (aOR 1.01; 95% CI 0.74–1.37), and births to women aged ≥40 years had a lower risk of defects (aOR 0.45; 95% CI 0.22–0.92). Defects were also elevated for nulliparity, anaemia, and urinary tract infection in births after ICSI, but not after IVF.

Conclusions The usual age–birth defect relationship is reversed in births after IVF and ICSI, and the associations for other maternal factors and defects vary between IVF and ICSI.

Keywords Birth defects, ICSI, Infertility, IVF, maternal factors.

Tweetable abstract Risk of birth defects in women over 40 years is lower after infertility treatment than for natural conceptions.

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Introduction

Treatment by assisted reproductive technology (ART), including *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), is an increasingly common strategy used to overcome infertility internationally.[1,2] It has become apparent that ART use is associated with an increased risk of birth defects, which varies by treatment modality.[3,4] The causal pathways that underlie these associations are not definitively understood in humans, although specific laboratory factors may contribute, including the embryo culture media, ICSI gamete manipulation, and returning embryos to the uterus soon after ovarian stimulation.[4,5]

In addition to potential treatment-related factors, parental health and lifestyle characteristics may also contribute to the excess risk of birth defects in couples using ART.

For example, compared with the fertile population, female recipients of ART are more likely to be older, obese, and have metabolic disease and chronic health conditions, including pre-existing diabetes and hypertension,[6] each of which is an independent risk factor for birth defects.[7–9] As a result of the contribution of these factors to infertility, studies have been largely unable to differentiate between the influence of ART treatment and parental characteristics on birth defects when comparing outcomes with a fertile population.[4,10] In addition, to our knowledge, no studies within the ART population have examined whether the established risk profiles for birth defects observed in the general population are similar among couples receiving ART, and whether they apply to both IVF and ICSI. As a result of the increasing use of ICSI for reasons other than severe semen defects,[11,12] it is important to consider the potential role of specific treatments independent of infertility aetiology. Accordingly, the objective of this study is to examine the degree to which maternal health and lifestyle factors are associated with the risk of birth defects after IVF and ICSI, adjusting for infertility aetiology and other potential confounding factors.

Methods

Study population

As detailed previously,[3] we linked data regarding all ART treatment cycles in South Australia for the period January 1986–December 2002 with the contemporary statewide perinatal outcomes data collection, and with the South Australian Birth Defects Register (SABDR). South Australia mandates the notification of all live births, terminations, and stillbirths of at least 20 weeks of gestation or 400 g birthweight using the Supplementary Birth Record. Terminations of pregnancy for congenital abnormalities before 20 weeks of gestation are also reported by law to the SABDR.

Maternal medical conditions (pre-existing and gestational) and reproductive history are recorded from antenatal records. We have restricted the present study to maternal factors alone, as paternal data are relatively sparse. Information on birth defects is collected up to the child's fifth birthday, beginning with reports at the time of birth or within 28 days of birth. For the present study, birth defects were classified according to the International Classification of Diseases (9th edition) and British Paediatric Association (ICD9-BPA) codes,[3] and only major abnormalities were included. Congenital cerebral palsy (CP), as defined by ICD9-BPA, was also routinely reported and was therefore included in the present study. As previously reported, CP contributes 0.4% of cases.[3] Please refer to our previous publication for the full definitions of defects, and inclusion and exclusion criteria.[3]

Statistical analyses

The unit of analysis used here is the birth of an individual (terminations of pregnancy for defects are included in this category). The current analysis was restricted to births conceived with IVF or ICSI conducted with fresh or frozen gametes or embryos, which were compared with each other, and with births conceived naturally (e.g. among the fertile population). The following maternal lifestyle factors were considered: maternal age at delivery, parity, body mass index (BMI) at first ART clinic visit (BMI is available only for women accessing ART), and smoking in early pregnancy. We also assessed maternal pre-existing conditions (hypertension, diabetes, asthma, and epilepsy) and gestational conditions [pregnancy-induced hypertension, including pre-eclampsia, impaired glucose tolerance (GT), gestational diabetes (GDM), anaemia, and urinary tract infection (UTI)]. For completeness, we also report outcomes for the small numbers of women with pre-existing diabetes and epilepsy, as although the risk estimates are unstable, these conditions were significantly associated with birth defects in the entire population of all births from which this cohort was drawn.[3]

Five variables used in this analysis had missing data, and there was evidence that it was not missing completely at random (MCAR).[13] The absence of data for two of the variables [parity and the Socio-Economic Indicators for Areas (SEIFA), a measure of economic disadvantage] could be ignored for this analysis, because the volume of missing data was small. Missing data for smoking, BMI, and to a lesser extent infertility diagnosis could not be ignored, however. Missing values for all five variables were imputed several times using regression models (linear or logistic as appropriate), with 100 imputations.[13,14] Sensitivity analyses were performed by varying the random number seeds and increasing the number of imputations in the multiply-imputed models. The results from the sensitivity analyses were similar to those presented in this paper. Associations between the presence of major birth defects and maternal health and lifestyle factors were expressed as adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs). We analysed the data using Bayesian logistic generalised estimating equations (GEEs), implemented via data augmentation, as we have a binary outcome with some sparse data.[15,16] We used weakly informative smoothing priors to stabilise the estimates. GEE modelling accounted for the clustering of births within women.

The role of maternal factors on the risk of birth defects was first considered separately for IVF, ICSI, and natural conceptions using three models. Model 1 was unadjusted. Model 2 included the year of treatment and the SEIFA small-area-aggregated index of relative disadvantage.[17] Model 3, the fully adjusted model, included the above, and

all other predictors, including maternal conditions. The models were then repeated among a pooled group of IVF and ICSI births, and then repeated to include comparison with the natural conception group across each risk factor stratum.

In a subsequent analysis we compared IVF with ICSI using three models. Model 1 included each maternal factor and the ART treatment details, including year of treatment, number of embryos transferred, and fresh- versus frozen-embryo transfer. Model 2 further adjusted model 1 for infertility aetiology. For the IVF group, the aetiology categories were: combined male and female infertility, male infertility only, endometriosis only, ovulatory infertility only, tubal infertility only, other and mixed aetiology female infertility, and idiopathic and unknown infertility aetiology. For the ICSI group, the aetiology categories were: male infertility only, female infertility only, and all other aetiologies. Model 3 included all of the maternal health and lifestyle variables in the same model, adjusted for all of the potential confounding factors (ART treatment details, SEIFA, and infertility aetiology).

We did not adjust for gestational age as this is likely to be in the causal pathway, either as a consequence of a birth defect or potentially as a mediator for certain specific defects; however, we did undertake models with and without adjustment for multiplicity. For this purpose, higher-order multiple pregnancies were combined with twins as they constituted a very small proportion of multiple pregnancies.[3] We did not adjust for multiple comparisons. In the tables we present data on the fully adjusted model only (e.g. model 3).

Table 1. Maternal health and lifestyle factors and pregnancy outcomes for all births arising from natural conception, IVF, or ICSI

	Natural conception *n* = 301 060 (%)	IVF *n* = 2211 (%)	ICSI *n* = 1399 (%)
Maternal age at delivery			
≤29 years	176 846 (58.7)	438 (19.8)	327 (23.4)
30–34 years	88 052 (29.3)	1014 (45.9)	648 (46.3)
35–39 years	31 170 (10.4)	647 (29.3)	361 (25.8)
≥40 years	4992 (1.7)	112 (5.1)	63 (4.5)
Nulliparity	113 313 (37.6)	1412 (63.9)	981 (70.1)
Maternal smoking in early pregnancy	85 994 (28.6)	452 (20.5)	210 (15.0)
Pre-existing conditions			
Hypertension	3357 (1.1)	23 (1.0)	19 (1.4)
Diabetes	896 (0.3)	8 (0.4)	5 (0.4)
Asthma	12 694 (4.2)	72 (3.3)	63 (4.5)
Epilepsy	1605 (0.5)	24 (1.1)	7 (0.5)
Gestational conditions			
PIH	26 305 (8.7)	252 (11.4)	165 (11.8)
Impaired GT	4830 (1.6)	77 (3.5)	27 (1.9)
GDM	3351 (1.1)	53 (2.4)	60 (4.3)
Anaemia	18 092 (6.0)	315 (14.3)	220 (15.7)
UTI	14 841 (4.9)	122 (5.5)	89 (6.4)
Singleton	293 692 (97.6)	1405 (63.6)	931 (66.6)
Pregnancy outcome			
Stillbirth	1682 (0.6)	39 (1.8)	21 (1.5)
Termination for defect	1497 (0.5)	10 (0.5)	9 (0.6)
Neonatal death	952 (0.3)	28 (1.3)	16 (1.1)
Survived neonatal period	296 929 (98.6)	2134 (96.5)	1353 (96.7)

Results

Pregnancy outcomes

Demographic and pregnancy characteristics for the study groups are presented in Table 1. There were 2211 IVF, 1399 ICSI, and 301 060 naturally conceived births. The percentage of women aged 35–39 and ≥40 years in the IVF and ICSI groups was more than double that of the fertile population. Nulliparity varied from 37.6% in the fertile group to 70.1% in the ICSI group. The rate of multiple pregnancy varied from 2.4% in the fertile group to 33.4% for ICSI and 36.4% for IVF, as the study included an early period when multiple-embryo transfer was common. The most common pre-existing health condition was asthma (3.3, 4.5, and, 4.2%, in IVF, ICSI, and natural conceptions, respectively), and the most common condition arising in pregnancy was anaemia (14.3, 15.7, and 6.0%, in IVF, ICSI, and natural conceptions, respectively). Most infants (over 96% in each group) were liveborn and survived the neonatal period.

Treatment-related factors for IVF and ICSI are presented in Table 2. Fresh-embryo transfer cycles were predominant for both IVF and ICSI groups.

Maternal demographic and lifestyle factors and birth defects

The unadjusted prevalence of any birth defect was 7.1% (n = 157) in the IVF group, 9.9% (n = 138) in the ICSI group, and 5.8% in the fertile population (n = 17 408). Multiple defects occurred in 2.3% of IVF births and 3.0% of ICSI births.

Relationships between maternal factors and risk of birth defects are presented in Table 3. In the left column are the maternal factors, followed by the count of subjects in each stratum, followed by the count and the percentage of defects in each stratum. These are followed by the fully adjusted models assessing the risk of birth defects. This is repeated for natural conceptions, IVF, and ICSI.

Table 2. Infertility aetiology, maternal BMI, and use of cryopreservation in births arising from IVF or ICSI

	IVF *n* = 2211 (%)	ICSI *n* = 1399 (%)
Infertility aetiology		
Male only	406 (18.4)	1049 (75.0)
Female only	1158 (52.4)	36 (2.6)
Endometriosis only	229 (10.4)	16 (1.1)
Ovulatory only	45 (2.0)	1 (0.1)
Tubal only	769 (34.8)	10 (0.7)
Mixed and other etiologies	115 (5.2)	9 (0.6)
Male and female combined	298 (13.5)	314 (22.4)*
Idiopathic and unknown aetiology	349 (15.8)	
Use of frozen embryo transfer	616 (27.9)	291 (20.8)
Maternal BMI		
≤24 kg/m^2	1429 (64.6)	820 (58.6)
25–29 kg/m^2	512 (23.2)	350 (25.0)
≥30 kg/m^2	270 (12.2)	229 (16.4)

*Idiopathic and unknown aetiology pooled with male and female combined due to small numbers.

For natural conceptions there was a monotonic increase in the prevalence of birth defects across categories of increasing age, from 5.6% for women aged ≤29 years to 8.2% for women aged ≥40 years. Relative to the reference group of women aged 30–34 years, women aged ≤29 years had a lower risk of defects (aOR 0.92; 95% CI 0.88–0.95), whereas women aged ≥40 years had a higher risk (aOR 1.49; 95% CI 1.33–1.66).

In contrast, the prevalence of birth defects after IVF was 9.4% for women aged ≤29 years, which declined to 3.6% for women aged ≥40 years. Within the IVF group, births to women aged ≤29 years had a significantly higher risk of birth defects compared with the reference group aged 30–34 years, which was robust to adjustment (aOR 1.55; 95% CI 1.01–2.38). A similar, but not statistically significant pattern was observed for ICSI, where the prevalence of birth defects was 11.3% for births to women aged ≤29 years, and 6.3% for births to women aged ≥40 years. Pooling the IVF and ICSI data indicated that relative to the reference group aged 30–34 years births to women aged ≤29 years had a higher risk of defects (aOR 1.42; 95% CI 1.04–1.94), there was no difference for women aged 35–39 years (aOR 1.01; 95% CI 0.74–1.37), and births to women aged ≥40 years had a lower risk of defects (aOR 0.45; 95% CI 0.22–0.92).

For natural conceptions, in the fully adjusted models nulliparity and smoking increased the risk of birth defects (aOR 1.19 and 1.04, respectively; 95% CI 1.15–1.23 and 1.01–1.08, respectively), as did pre-existing diabetes (aOR 2.17; 95% CI 1.76–2.67), asthma (aOR 1.14; 95% CI 1.05–1.22), epilepsy (aOR 1.69; 95% CI 1.42–2.01), and anaemia (aOR 1.15; 95% CI 1.08–1.23; Table 4). Although UTI was significantly associated with defect risk in

Table 3. Odds ratios for any birth defect by maternal demographic and lifestyle factors among births arising from natural conception, IVF, or ICSI

	Natural conception (*n* = 301 060)			IVF (*n* = 2211)			ICSI (*n* = 1399)		
	All *n*	Defects* *n*, %	Adjusted model** OR (95% CI)	All *n*	Defects* *n*, %	Adjusted model** OR (95% CI)	All *n*	Defects* *n*, %	Adjusted model** OR (95% CI)
Age (years)									
≤29	176 846	9904, 5.6	**0.92 (0.88–0.95)**	438	41, 9.4***	**1.55 (1.01–2.38)**	327	37, 11.3	1.07 (0.68–1.68)
30–34	88 052	5087, 5.8	Ref.	1014	62, 6.1	Ref.	648	64, 9.9	Ref.
35–39	31 170	2007, 6.4	**1.14 (1.08–1.21)**	647	50, 7.7	1.28 (0.86–1.92)	361	34, 9.4	1.01 (0.64–1.59)
≥40	4992	410, 8.2	**1.49 (1.33–1.66)**	112	4, 3.6	0.63 (0.24–1.69)	63	4, 6.3	0.72 (0.26–1.97)
Parity									
0	113 313	7149, 6.3	**1.19 (1.15–1.23)**	1412	99, 7.0****	0.92 (0.63–1.36)	981	112, 11.4***	**2.08 (1.25–3.44)**
1	108 671	5944, 5.5	Ref.	576	43, 7.5	Ref.	341	21, 6.2	Ref.
≥2	79 077	4316, 5.5	**0.95 (0.91–0.99)**	223	15, 6.7	0.91 (0.48–1.71)	77	6, 7.8	1.31 (0.50–3.40)
Smoker									
Yes	85 994	5057, 5.9	**1.04 (1.01–1.08)**	452	42, 9.3****	1.45 (0.98–2.13)	211	15, 7.3	0.69 (0.39–1.23)
No	215 066	12 351, 5.7	Ref.	1759	115, 6.5	Ref.	1189	124, 10.4	Ref.

*Row percentage.
**Includes adjustment for year of birth, SEIFA, and all other maternal health and lifestyle factors (model 3).
***Significantly different in comparison with natural conceptions (model 3).
****Significantly different in comparison between IVF and ICSI conceptions in model with adjustment for year of treatment, SEIFA, embryo transfer status (fresh/frozen), infertility aetiology, and all other maternal health and lifestyle factors (model 3).
Text in bold indicates a statistically significant finding.

Table 4. Odds ratios for any birth defect by maternal medical conditions (pre-existing and gestational) among births arising from natural conception, IVF, or ICSI

	Natural conception (*n* = 301 060)			IVF (*n* = 2211)			ICSI (*n* = 1399)		
	All *n*	Defects* *n*, %	Adjusted model** OR (95% CI)	All *n*	Defects* *n*, %	Adjusted model** OR (95% CI)	All *n*	Defects* *n*, %	Adjusted model** OR (95% CI)
Hypertension									
Yes	3357	221, 6.6	1.07 (0.93–1.24)	23	1, 4.3	0.87 (0.28–2.69)	19	4, 21.1	2.42 (0.76–7.74)
No	297 703	17 187, 5.8	Ref.	2188	156, 7.1	Ref.	1380	135, 9.8	Ref.
Diabetes									
Yes	896	112, 12.5	**2.17 (1.76–2.67)**	8	1, 12.5	1.25 (0.35–4.45)	5	1, 20.0	1.16 (0.33–4.07)
No	300 164	17 296, 5.8	Ref.	2203	156, 7.1	Ref.	1394	138, 9.9	Ref.
Asthma									
Yes	12 694	841, 6.6	**1.14 (1.05–1.22)**	72	8, 11.1	1.75 (0.80–3.83)	63	7, 11.1	1.04 (0.45–2.38)
No	288 366	16 567, 5.8	Ref.	2139	149, 7.0	Ref.	1336	132, 9.9	Ref.
Epilepsy									
Yes	1605	155, 9.7	**1.69 (1.42–2.01)**	24	3, 12.5	1.51 (0.49–4.66)	7	0, 0.0	0.78 (0.25–2.45)
No	299 455	17 253, 5.8	Ref.	2187	154, 7.0	Ref.	1392	139, 10.0	Ref.
Anaemia									
Yes	18 092	1207, 6.7	**1.15 (1.08–1.23)**	315	23, 7.3	1.05 (0.65–1.69)	220	32, 14.5	**1.64 (1.03–2.61)**
No	282 968	16 201, 5.7	Ref.	1896	134, 7.1	Ref.	1179	107, 9.1	Ref.
UTI									
Yes	14 841	932, 6.3	1.06 (0.99–1.14)	122	8, 6.6	0.96 (0.45–2.03)	89	18, 20.2***	**2.31 (1.27–4.20)**
No	286 219	16 476, 5.8	Ref.	2089	149, 7.1	Ref.	1310	121, 9.2	Ref.
BMI**									
<25	–	–	–	1429	81, 5.7	Ref.	820	72, 8.7	Ref.
25–29	–	–	–	512	45, 8.7	**1.64 (1.10–2.44)**	350	44, 12.6	1.41 (0.93–2.15)
30+	–	–	–	270	32, 11.7	**2.09 (1.31–3.34)**	229	24, 10.3	1.19 (0.71–2.00)

*Row percentage.
**Includes adjustment for year of birth, SEIFA, and all other maternal health and lifestyle factors (model 3).
***Significantly different for comparison with natural conceptions (model 3).
****BMI is not available for natural conceptions. For BMI, the model is adjusted for year of treatment, SEIFA, embryo transfer status (fresh/frozen), infertility aetiology, and all other maternal health and lifestyle factors (model 3).
Text in bold indicates a statistically significant finding.

models 1 and 2, this association was attenuated in the fully adjusted model (aOR 1.06; 95% CI 0.99–1.14). Pre-existing hypertension (OR 1.14, 95% CI 1.00–1.31) was significantly associated with risk only in the unadjusted model and was not significant after adjustment. Gestational diabetes, impaired glucose tolerance, and pregnancy-induced hypertension were not significant risk factors in any model and are not presented.

For the IVF group, in addition to maternal age ≤29 years, significant risk factors for birth defects in the fully adjusted model (model 3) were being overweight (aOR 1.64; 95% CI 1.10–2.44) or being obese (aOR 2.09; 95% CI 1.31–3.34). Pre-existing conditions and obstetric conditions were not significant risk factors in any IVF model (Table 4).

For the ICSI group, in the fully adjusted models, significant risk factors for birth defects included nulliparity (aOR 2.08; 95% CI 1.25–3.44), anaemia (aOR 1.64; 95% CI 1.03–2.61), and urinary tract infection (aOR 2.31; 95% CI 1.27–4.20; Table 4).

The risk estimates did not vary appreciably across models for either ART treatment group or natural conceptions when there was adjustment for multiplicity.

IVF versus ICSI

The relationships between maternal factors and the risk of birth defects were not identical between IVF and ICSI births. With regards to nulliparity, the risk of birth defects for the IVF group was significantly lower than that for the ICSI group in all models (aOR 0.45; 95% CI 0.24–0.85; data not shown). In contrast, among smokers, the risk of birth defects was significantly higher in the IVF groups compared with the ICSI group (aOR 2.12; 95% CI 1.06–4.24; data not shown).

Discussion

Main findings

We believe that this is the first study to examine the independent effects of maternal demographic, lifestyle, and medical factors in an ART population by treatment modality. The present study shows that established maternal risk factors for defects in the fertile population do not necessarily follow the same pattern in births following ART treatment, and that the profile of risk factors varies by ART treatment type. In contrast to the fertile population, in which children of older mothers had a higher risk of birth defects, in infertile women treated with IVF, the greatest risk was among the youngest women (≤29 years), who had over double the rate of birth defects compared with their oldest counterparts, and a significantly higher rate than age-matched peers in the fertile population. Adjustment for infertility aetiology and other maternal factors did not change this association. A similar pattern was seen when IVF and ICSI were combined, with the highest risk observed in young women, grading down to an odds ratio of 0.45 in aged women 40 years and older. This finding directly contradicts the untested assertion that the older age of women undergoing ART treatment is the primary cause of any observed increase in birth defects.[18]

Strengths and limitations

The main strength of this study is that we have nearly a complete ascertainment of mode of conception for an entire state population, with birth defects ascertained to 5 years of age. We also adjusted for treatment-related factors, multiplicity, and infertility aetiology; however, we cannot be certain whether conditions arising in pregnancy (UTI and anaemia) are the cause or consequence of the adverse outcomes associated with ART. Furthermore, as this study required multiple comparisons within the same population, we cannot preclude that some statistically significant findings occurred by chance, which reinforces the value of replicating these observations in another population. Another limitation is the absence of information on paternal characteristics, as these data are not routinely recorded in maternity records. The most recent data are from 2002. Nevertheless, the clinical factors studied remain in use internationally and clinical outcomes have not varied greatly in the intervening years.

Interpretation

As we adjusted for infertility aetiology, our findings support the possibility of an unknown factor(s) contributing to defect risk. Although there may be a contribution from some unmeasured patient-related factors to the elevated risk in young women, we know of no potential confounding factor that could reduce the risk by more than half in older women treated with ART compared with either younger women with infertility or age-matched peers in the fertile population. This implies that a previously undescribed protective mechanism is in action, the details of which we can only speculate. As all women in the ART groups received ovulation induction drugs and invasive treatment involving gamete manipulation, one possibility is that IVF and ICSI may generate embryos with an increased risk of birth defects, and such embryos may be more likely to survive in the uterine environment of a younger rather than an older mother; however, this cannot explain the very low prevalence of birth defects observed in IVF births to women aged 40+ years (3.6%), compared with their fertile age-matched peers (8.2%). Although aneuploidy increases with age for reasons that are incompletely understood, and which are presently uncontrollable, the resumption of meiosis in the ovary occurs under the influence of gonadotropins,[19] which raises the prospect that through an unknown process the administration of gonadotropins in older women might provide a protective effect on the oocyte during meiosis. Alternatively, some presently unknown but common factor related to diminished fertility in older women may be strongly protective against birth defects should fertilisation occur.

Further research will be needed studying pregnancies with donor embryos, and using markers of embryo quality by age, to resolve the apparent age paradox. Nevertheless, it should be of interest to older women seeking ART to note that they may be at less risk of major birth defects than their fertile age-matched peers. Unfortunately, young women may have a higher risk of birth defects relative to older infertility patients or fertile age-matched peers; thus, we urgently need to identify modifiable risk factors for this group.

Among pregnancies conceived with IVF, smoking in pregnancy and being overweight or obese elevated the risk of defects, whereas pre-existing and gestational health conditions did not. These associations are consistent with risks reported in the general fertile population.[7,20] BMI was not available for the fertile population for this study, however, and represents a knowledge gap for subsequent study.

In contrast, in ICSI pregnancies, nulliparity, anaemia, and urinary tract infection were associated with birth defects, and maternal BMI was not. With the exception of anaemia, these associations have been reported in the general population.[8,9,21–23] The pattern of associations between maternal factors and birth defects diverged for IVF and ICSI, with a significantly elevated risk associated with nulliparity in ICSI compared with IVF. Although smoking was a risk factor for birth defects in the IVF group, it appeared to be protective in the ICSI group.

We hypothesise that the restriction of risk associated with nulliparity and infection to the ICSI group may reflect an ICSI-specific effect on the maternal immune system. In

rodent models, ICSI can result in a pro-inflammatory state with increased placental concentrations of reactive oxygen species and inflammatory cytokines.[24] During a first pregnancy, the maternal immune system adapts to accommodate the fetus by learning to recognise fetal antigens. In subsequent pregnancies, maternal tolerance of the fetus is reflected in altered maternal cytokine profiles, decreased risk of inflammatory diseases such as pre-eclampsia, chronic hypertension, and anaemia,[25–27] and increased risk of infection.[28] Thus, the cluster of associations observed here for ICSI may reflect a state of maternal immune maladaptation to early pregnancy. This warrants further directed research.

The increased birth defect risk associated with smoking after IVF compared with ICSI may also be informative with regards to the maternal response to an ICSI conceptus, as the risk of certain inflammatory conditions of first pregnancy, such as pre-eclampsia, is reduced by smoking.[29,30]

Conclusion

Congenital anomalies are a major cause of stillbirth and neonatal deaths, and have enduring consequences for the health of surviving infants. This study demonstrates that the contribution of maternal demographic, health, and lifestyle characteristics to the risk of major birth defects varies by mode of conception. The inverse association of birth defects with maternal age after assisted conception, particularly among IVF pregnancies, contradicts the assumption that older maternal age is the cause of an observed excess of birth defects in pregnancies resulting from IVF and ICSI. It also raises important questions for further research on whether the established age–birth defect relationship can be modified. We also observed that the association between maternal risk factors and birth defects varied between IVF and ICSI for parity and smoking, which may indicate differences in the maternal response to the conceptus. Some treatment subgroups within the ART population may require closer monitoring or targeted medical management: the doubled birth defect risk in nulliparous women after ICSI but not after IVF is important, as ICSI is now the preferred method of fertilisation across all regions of the world,[12] even in the absence of male-factor infertility.[11] Research should be directed to determining how IVF and ICSI procedures contribute to, and interact with, maternal health status in the aetiology of birth defects.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

MD conceived the study question. MD, VM, and JM were responsible for the design of the study. KW undertook the statistical analyses. MD, AR, and JM developed the first draft of the article, and all authors, including ML, WS, LM, JT, LG, and MW contributed to the interpretation of findings and revising of drafts of the article. All authors approved the final article for publication and agree to be accountable for the content.

Details of ethics approval

Approval for the study was obtained from the ethics committees of the South Australian Department of Health Human Research Ethics Committee (ref. no. 19 012 006), the University of Adelaide Human Research Ethics Committee (ref. no. H-002-2005), and Flinders Clinical Research Ethics Committee (ref. no. 78/02). Individual-level consent was not required as all data were de-identified.

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