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Original Research Article

The Risks of Birth Defects with Conception by ART (Assisted Reproductive Technology)

Monica Singh[1], Rashmi Vishwakarma[2], Ankur Singhai[3], Randhir Singh[4]

[1]Associate Professor, Department of Obstetrics & Gynaecology, LN Medical College, Bhopal, MP
[2,3,4]Associate Professor, Department of Paediatrics, LN Medical College, Bhopal, MP

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Corresponding author: Dr. Randhir Singh
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Abstract:

Objective: To find out association between fertility status, method of conception and the risks of birth defects.

Methods: This was a population-based cohort study linking ART cycles. from 1 January 2019 to 31 December 2022 that resulted in live births in 2020-2022. Non-ART siblings were identified through the birth history. Children from non-ART births were classified as being born to women who conceived with no ART treatment and were classified as being naturally conceived.

Results: A total of 02 singleton children (2.04%) and 03 twin children (3.06%) had a major birth defect (chromosomal or nonchromosomal). Children conceived with ART from autologous oocytes had increased risks for nonchromosomal defects, including blastogenesis, cardiovascular, gastrointestinal and, for males only, genitourinary defects, with AORs ranging from 1.08 to 1.12; children in the autologous-fresh group also had increased risks for musculoskeletal and orofacial defects. Within the donor oocyte group, the children conceived from fresh embryos did not have increased risks in any birth defect category, whereas children conceived from thawed embryos had increased risks for nonchromosomal and blastogenesis defects.

Conclusion: The risk of birth defects had two independent components: (i) method of conception and (ii) presence, type and number of birth defects.

Keywords: In vitro fertilization (IVF) / Assisted Reproductive Technology (ART) / Birth Defects / Singletons / Twins / Oocyte Source / Embryo Stage / Siblings.

Introduction

The rarity of the co-occurrence of birth defects and ART makes studying their association challenging. Prior studies have indicated that infertility and ART are associated with an increased risk of birth defects or cancer but have been limited by small sample size and inadequate statistical power, failure to adjust for or include plurality, differences in definitions and/or methods of ascertainment, lack of information on ART treatment parameters or study periods spanning decades resulting in a substantial historical bias as ART techniques have improved.

Materials and Methods

The study population included 98 ART children, 96 non-ART siblings, all study children were investigated to identify major defects diagnosed within the first year of life. We classified children with major defects as either chromosomal (i.e. presence of a chromosomal defect with or without any other major defect) or nonchromosomal (i.e. presence of a major defect but having no chromosomal defect), or all major defects (chromosomal and nonchromosomal), and calculated rates per 1000 children. All study children were also linked to their respective State cancer registries. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs of cancer by birth defect status (including presence of a defect, type and number of defects), and conception group.

Only in-state deliveries are included in this study. Mothers may have more than one birth, all live births would be classified as ART. For each ART-conceived delivery, we requested that the subsequent 10 deliveries (all liveborn infants from a pregnancy) be selected as the non-ART comparison group. Each study child (naturally conceived, OI/IUI-conceived, non-ART siblings and ART-conceived) was then linked to their respective State's birth defects registry and cancer registry.

Birth Defects: For this study, we analyzed selected major birth defects diagnosed within the first year of life. We then classified individuals with major birth defects as either 'chromosomal' (i.e. presence of a chromosomal defect with or without any other major defect) or 'nonchromosomal' (i.e. presence of a major defect but having no chromosomal defect). Of

the families that were identified, only 0.4% of the families of children with birth defects had more than one delivery where a birth defect was reported.

Blastogenesis Defects

We chose also to include birth defects classified as a group as blastogenesis defects, defined on the basis of pathologic development rather than by organ system. This allowed us to define defects that were expected to originate within the first 4 weeks of gestation, excluding cardiac defects, which we evaluated separately

Defects in Twin Pairs

We examined the incidence of birth defects in twins and found that the rate of twins both having a major birth defect or both having the same type of birth defect (except central nervous system (CNS)) was greater than expected at random. We compared the estimates of the odds ratios using all the data with the odds ratios after excluding the second twin

Conception Groups

As described above, four groups of births were defined based on the absence/presence of subfertility/infertility and the method of conception. The non-ART comparison group births were categorized as naturally conceived or OI/IUI. The other two groups were ART and their non-ART siblings. The ART births were further divided into four subgroups depending on the combination of oocyte source (autologous or donor) and embryo state (fresh or thawed), based on our prior analyses indicating associations of these combinations with adverse perinatal outcomes, including birth defects.

Independent Variables

Independent variables were selected a priori for inclusion in the models based on established associations with birth defects, cancer and/or ART. These included paternal age at delivery, race, Hispanic ethnicity, education, parity, BMI (weight/height calculated from height and pre-pregnancy weight reported on the birth certificate, diabetes (pregestational and/or gestational), hypertension and infant sex, plurality (singleton or twin) as well as State and year of birth.

ART factors and treatment parameters included infertility); the use of ICSI (which was only available for fresh IVF cycles); sperm source was limited to partner. Singleton and twin births were analyzed together, with a variable of plurality in the models, indicating the risk of twins compared to singletons. Triplets and higher order multiples were excluded.

Observation Chart

Table 1 Characteristics of the study population: singleton births.

		Naturally conceived	OI/IUI conceived	Non-ART siblings	ART by oocyte source and embryo state			
					Autologous		Donor	
					Fresh	Thawed	Fresh	Thawed
	All children, N	1 315 497	8875	30 036	55 494	33 835	7162	4828
Maternal Race	White	74.7	85.2	85.7	82.9	78.4	83.5	81.7
(%)	Black	16.7	5.3	4.9	6.0	6.7	6.9	7.8
	Asian	8.6	9.5	9.5	11.0	14.9	9.6	10.5
	Other/missing	*7.4*	*2.7*	*2.9*	*2.6*	*3.1*	*3.2*	*2.9*
Maternal Ethnicity (%)	Hispanic	28.5	9.5	10.9	11.5	9.8	11.4	10.9
Maternal age	Mean years (SD)	29.1 ± 5.8	33.7 ± 5.0	33.4 ± 4.8	34.9 ± 4.2	35.2 ± 4.2	42.2 ± 4.8	42.8 ± 5.3
(%)	18–29	52.1	20.3	19.8	10.4	8.8	1.3	1.6
	30–34	29.0	37.3	37.6	35.9	35.1	6.5	6.1
	35–37	11.2	20.3	22.6	25.2	26.5	8.0	8.3
	38–40	5.5	13.1	13.9	18.8	19.0	15.2	12.8
	41–43	1.8	6.5	4.8	8.8	8.8	24.9	21.0
	≥44	0.3	2.5	1.1	0.9	1.8	44.1	50.2
Paternal age	Mean years (SD)	31.9 ± 6.8	35.7 ± 6.2	35.6 ± 5.7	37.3 ± 5.9	37.7 ± 5.9	42.8 ± 6.6	43.5 ± 7.0
(%)	18–34	66.9	46.2	43.9	34.1	30.5	9.9	9.1
	35–40	23.0	34.8	38.6	40.8	42.9	26.9	25.4
	≥41	10.1	19.1	17.4	25.1	26.6	63.2	65.5
	Missing	*10.9*	*5.7*	*2.0*	*0.7*	2.2	*1.2*	*8.5*
Maternal Education (%)	<High school	15.1	1.7	1.9	1.3	1.8	1.5	1.4
	High school graduate	24.2	8.0	8.0	7.6	5.7	6.5	5.9
	Some college/Assoc. Degree	27.5	21.5	17.4	19.9	18.4	19.1	20.4
	Bachelor's degree	20.2	34.7	38.3	38.2	38.6	38.1	36.7
	Post-graduate degree	13.0	34.2	34.5	33.1	35.5	34.8	35.7
	Missing	*1.3*	*0.3*	*1.5*	*1.3*	*1.0*	*1.4*	*1.2*
Parity (%)	0	40.6	64.6	44.1	69.4	55.2	69.5	52.3
	1	32.7	26.9	32.8	23.4	32.7	21.9	32.9
	≥2	26.7	8.6	23.0	7.2	12.2	8.7	14.7
BMI (kg/m^2)	Mean (SD)	26.3 ± 6.3	26.6 ± 6.5	24.4 ± 5.1	25.2 ± 5.5	25 ± 5.4	25.2 ± 5.3	25.5 ± 5.6
(%)	12–24	51.4	51.1	65.6	59.5	61.0	58.7	56.6
	25–29	25.8	24.2	21.4	23.4	22.9	24.8	25.6
	30–59	22.8	24.7	13.0	17.1	16.1	16.4	17.7
	Missing	*36.8*	*36.4*	*42.6*	*44.9*	*20.8*	*42.7*	*28.3*
Diabetes (%)	Pre-gestational or gestational	5.7	10.0	5.4	7.3	8.2	8.9	10.0
Hypertension (%)	Pre-gestational or gestational	5.8	9.7	5.1	6.7	9.1	13.0	14.0
Length of gestation	Mean weeks (SD)	38.7 ± 1.9	38.5 ± 2.3	38.6 ± 2	38.4 ± 2.2	38.5 ± 2.2	38.2 ± 2.3	37.9 ± 2.4
(%)	<28 weeks	0.5	0.9	0.8	0.7	0.7	0.7	1.1
	28–32 weeks	1.1	1.8	0.9	1.7	1.4	2.2	2.5
	33–36 weeks	6.1	7.4	6.3	8.5	8.0	12.1	12.4
	≥37 weeks	92.4	89.8	92.0	89.0	89.8	85.0	84.0
Birthweight	Mean g (SD)	3310 ± 554	3285 ± 623	3339 ± 565	3235 ± 601	3369 ± 602	3233 ± 634	3221 ± 652
(%)	300–999 g	0.5	0.9	0.7	0.8	0.7	0.7	1.1
	1000–1499 g	0.5	1.0	0.4	0.9	0.7	1.4	1.0
	1500–2499 g	5.0	6.2	4.5	7.3	5.2	8.5	9.2
	≥2500 g	94.0	91.9	94.4	91.0	93.5	89.4	88.7

(continued)

Table 2: Rates And Risks Of Birth Defects By Method Of Conception				
Naturally OI/IUI Non-ART ART by oocyte source and embryo state Plurality Sex Plurality Conceived Siblings Twins vs Males vs singletons females Fresh Thawed Fresh Thawed			Autologous	Donor
Type of defect, Major defect** (Nonchromosomal)	Rate****	Singletons Twins	18.4 34.1	21.9 33.8
	AOR		1	1.21
	95% CI		Reference	1.08, 1.36
Blastogenesis	Rate	Singletons	2.2	1.9
		Twins	3.1	4.5
	AOR		1	1.28
	95% CI		Reference	0.90, 1.82
Cardiovascular	Rate	Singletons	10.4	9.8
		Twins	22.3	17.6
	AOR		1	1.04
	95% CI		Reference	0.88, 1.23
Central nervous system	Rate	Singletons	0.4	0.2
		Twins	0.7	0.8
	AOR		1	1.05
	95% CI		Reference	0.43, 2.57
Gastrointestinal	Rate	Singletons	0.9	1.6
		Twins	1.4	2.8
	AOR		1	2.01
	95% CI		Reference	1.32, 3.07
Musculoskeletal	Rate	Singletons	2.9	3.3
		Twins	4.3	5.0
	AOR		1	1.26
	95% CI		Reference	0.94, 1.69
Genitourinary (males only)	Children,	Singletons Twins		

Results

A total of 02 singleton children (2.04%) and 03 twin children (3.06%) had a major birth defect (chromosomal or nonchromosomal). Children conceived with ART from autologous oocytes had increased risks for nonchromosomal defects. Within the donor oocyte group, the children conceived from fresh embryos did not have increased risks in any birth defect category, whereas children conceived from thawed embryos had increased risks for nonchromosomal defects (AOR 1.20, 95% CI 1.03, 1.40) and blastogenesis defects.

Risk of birth defects by mode of conception: Compared to naturally conceived children, risks for defects were increased for all other groups for nonchromosomal Orofacial defects were increased in the OI/IUI and autologous-fresh and autologous-thawed groups (AORs 1.26–1.42). As expected, chromosomal defects were lower in the donor-fresh and donor-thawed groups (AORs 0.06–0.08), but also in the autologous-thawed group (AOR 0.61). Approximately 81% of children with a chromosomal defect had Down syndrome. Twins had greater risks compared to singletons in every birth defect category except orofacial and chromosomal, with AORs ranging from 1.26 to 1.76. Males had greater risks than females for nonchromosomal, blastogenesis, musculoskeletal and orofacial defects, with AORs ranging from 1.16 to 1.50 and lower risks for cardiovascular defects.

Risk of childhood cancer by mode of conception: The rates of all cancers, leukemia, CNS tumors, embryonal tumors and solid tumors, and the results of the Cox proportional hazards regression models are shown in Table V. The naturally conceived group had 1469 of the 1789 cancers, the ART autologous groups 165 and 50 cancers, the non-ART siblings 59 cancers and the three smallest groups had 19, 16 and 9 cancers; The risk of solid tumors was increased in the ART autologousfresh group (HR 1.39). As a sensitivity analysis, the analysis was repeated excluding all children with a major birth defect (see Supplementary Table SIII); the HRs were of a similar magnitude, although some did not achieve significance due to the >40% reduction in sample size.

Risk of cancer as a function of birth defect status A total of 127 children had both birth defects and cancer, of which 53 (42%) had leukemia. The two components of the risk of cancer are independent

and therefore, on the average, their coefficients are multiplicative.

Statistical Analysis:

Data from each patient were processed to generate a common dataset. Logistic regression models were used to generate adjusted odds ratios (AORs) and 95% CIs of the risk of birth defects by conception group with naturally conceived children as the reference, adjusted for paternal and maternal ages; maternal race and ethnicity, education, BMI, parity, diabetes, hypertension; and for plurality, infant sex and State and year of birth. We excluded children whose mother or father was younger than 18 years of age, unknown sex of child or implausible values (gestational age <22 weeks or birthweight <300 g even if indicated as a live birth). Because most independent variables were categorized, missing values were included as a separate category for maternal BMI, education and race, and father's age. There were no missing data for other variables.

Discussion

This study presents contemporary, population-based findings in three important areas of child health: birth defects, childhood cancer, and their co-occurrence among children who were conceived naturally, with OI/IUI, and with ART by oocyte source and embryo state, building upon findings from our prior analyses in these areas.

In their population-based study from Australia, Dawson et al. reported three significant associations after these known birth defect-cancer exclusions: cardiovascular defects with cancer, birth defects with hepatic tumors and leukemias other than acute lymphocytic leukemia and acute myeloid leukemia (HR 4.30, 95% CI 1.23, 15.09). Although not feasible to ascertain in the current study because of small numbers of children with both birth defects and cancers, prior studies have reported elevated risks of anomalies and malignancies within the same organ system, including neurological defects and CNS tumors; congenital anomalies of the kidney and urinary tract and urinary tract cancer; eye defects and retinoblastoma, and gastrointestinal defects and hepatoblastoma.

Art and Birth Defects and Cancer: Fertility is strongly related to age, for both male and female partners, which can be seen in the differences in the conception groups in this study. The increased birth defect risk in the OI/IUI, nonART siblings, and ART autologous-fresh and thawed groups suggests an association with underlying parental subfertility, while the increased risk in the donor-thawed versus the donor-fresh group may be associated with the process of cryopreservation.

The pattern of elevated cancer risk for both non-ART siblings and children in the ART autologous-fresh group suggests common genetic and/or environmental factors. Blastogenesis defects and embryonal tumors have relevance to ART. Our analysis indicated that, compared to the naturally conceived group, the risks of blastogenesis defects and cardiovascular defects were increased in all the other six conception groups. Embryonal tumors have been hypothesized to be associated with developmental disruptions, thereby sharing pathophysiologic features with birth defects. Our analyses indicate that the risk of embryonal tumors increases in the presence of nonchromosomal defects, also reflecting developmental disruption in the periconceptual period, when the epigenome is most

Sibling Risks: The choice of an appropriate comparison group in infertility research poses a special challenge. Although most studies compare women treated for infertility to fertile women, this approach has several potential disadvantages, including differences in age, socioeconomic status, education and reproductive history. Comparisons within families, as repeat pregnancies to the same woman, have the advantage of eliminating the fixed effects of the parents (mainly the genetic contribution), with adjustments possible for her change in age, parity and, if appropriate, method of conception. In our prior studies of siblings in Massachusetts, declining fertility status, with or without ART treatment, was associated with increasing risks for adverse outcomes, greatest for women whose fertility status declined the most between the two pregnancies

Strengths: This study has a number of strengths, including a sample size, population-based design, and contemporary time period. Our live birth prevalence rates of birth defects are in accord with both US and European rates, as well as our prior research in Massachusetts. Our findings of higher birth defects rates among twins compared to singletons are also in accord with prior studies. The data on infertility, birth outcomes, cancer and birth defects were independently collected, minimizing the risk of ascertainment bias.

Limitations: This study must be considered considering certain limitations. It was not possible to differentiate embryo freezing done at which day of cleavage stage and data on ICSI was only available in the fresh embryo ART group; and data were unavailable on duration of infertility, which has been reported to be related to birth defect risk. Data on preimplantation testing were not available, other than the infertility diagnosis of preimplantation genetic diagnosis. For the OI/IUI group, it was not possible to differentiate type of non-ART treatment utilized. Data on birth defects were not available on miscarriages, terminations, or stillbirths, only on live births; this limitation is also noted in other population-based studies, which for legal reasons could not be included in the linkages or analyses.

This limited our ability to study conditions that are more likely to be terminated after prenatal detection. In addition, data were unavailable on imprinting disorders. These findings indicate that children conceived with ART, non-ART siblings, and all children with birth defects should be monitored more closely for the subsequent development of cancer.

Conclusion

Total of 02 singleton children (2.04%) and 03 twin children (3.06%) had a major birth defect (chromosomal or nonchromosomal). Among both naturally conceived and ART-conceived children, the presence of birth defects was associated with a greater risk of cancer. This information regarding birth defects and future cancer risk should be included when counseling patients about the risks and benefits of ART,

What we learnt from the Study

The use of ART is associated with increased risks of major nonchromosomal birth defects. The presence of birth defects is also associated with greater risks for cancer, which adds to the baseline risk in the ART group. Although this study does not show causality, these findings indicate that children conceived with ART, non-ART siblings, and all children with birth defects should be monitored more closely for the subsequent development of cancer.

Limitations of the Study

It was not possible to differentiate day and cell stage of embryo freezing, and data on ICSI were only available in the fresh embryo ART group. It was not possible to differentiate type of non-ART treatment utilized, and in both the ART and and natural NON-ART births, data were unavailable on duration of infertility.

Since OI/IUI is underreported on the birth certificate, some OI/IUI children were likely included among the naturally conceived children, which will decrease the difference between all the groups and the naturally conceived children. All children should also be monitored more closely for the subsequent development of cancer.

Declarations:

Availability of data and material: Department of Pediatrics and Department of Obstretrics & Gynaecology LN Medical College, Bhopal **Code availability**: Not applicable **Consent to participate**: Consent taken. **Ethical Consideration**: There are no ethical conflicts related to this study. **Consent for publication**: Consent taken

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