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ORIGINAL RESEARCH ARTICLE

Prevalence of structural birth defects in IVF-ICSI pregnancies resulting from autologous and donor oocytes in Indian sub-continent: Results from 2444 births

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Abstract

Introduction: This study was conducted to evaluate and compare the incidence of birth defects in In-Vitro Fertilization-Intra Cytoplasmic Sperm Injection (IVF-ICSI) pregnancies with autologous and donor oocytes. As a secondary outcome, the prevalence of birth defects in IVF-ICSI pregnancies was compared with those from spontaneous conceptions in India.

Material and methods: This retrospective study included 2444 births resulting from IVF-ICSI cycles from autologous (n = 1743) and donor oocytes (n = 701) during a 3-year period in an Indian infertility center. Birth defects, if any, were noted antenatally and followed till the neonatal period, in case of live birth.

Results: The overall prevalence of birth defects in IVF-ICSI pregnancies in this study was 29/2444 (118.6/10 000 births) and the most common congenital anomaly was cardiac malformation (32.7/10 000 births) followed by genitourinary (28.6/10 000 births). The risks of birth defects resulting from autologous and donor oocytes did not differ (114.7/10 000 vs 128.38/10 000; $P > 0.05$). However, pregnancies resulting from autologous oocytes had a higher trend of gastrointestinal birth defects (20.5/10 000 births vs 0), though not statistically significant. The risk of cardiovascular birth defects resulting from IVF-ICSI pregnancies was much higher compared with the natural conceptions in India (32.7/10 000 vs 12.7/10 000 births; $P = 0.03$), whereas the risk of central nervous system malformations was much lower (8.1/10 000 vs 60.18/10 000 births; $P = 0.005$).

Conclusions: Overall, there was no significant difference in birth defects resulting from IVF-ICSI with autologous or donor oocytes. The births resulting from IVF-ICSI pregnancies did not tend to have a higher rate of birth defects a compared with natural conceptions. The differences in the prevalence of certain birth defects (cardiovascular or central nervous system) reported in IVF-ICSI pregnancies may be due to improved surveillance modalities and early detection in pregnancies following

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; ET, embryo transfer; EUROCAT, European Concerted Action on Congenital Anomalies and Twins; ICSI, Intra Cytoplasmic Sperm Injection; IVF, In Vitro Fertilization; NNPD, National Neonatal and Perinatal Database; OR, odds ratio; RR, relative risk; SEARO, South East Asia Regional Office; WHO, World Health Organization.

IVF-ICSI. A study with larger number of sample size will give us better understanding of the prevalence of reported incidence in this study.

KEYWORDS
autologous oocytes, birth defects, congenital anomaly, donor oocytes, In Vitro Fertilization, Intracytoplasmic Sperm Injection

1 | INTRODUCTION

The Tenth Revision of the International Classification of Diseases (ICD10) defines congenital anomalies as congenital malformations, deformations and chromosomal abnormalities, but exclude inborn errors of metabolism. An estimated 8 million children are born annually worldwide (accounting for 6% of total births) with serious birth defects.[1] In addition; there are birth defects of post-conception origin resulting from maternal exposure to teratogens, infections and nutritional deficiencies that can harm a developing fetus. There are many attributing causes to birth defects which include maternal age, medical conditions such as diabetes and environmental factors.

The association of assisted reproductive technology (ART) and the risk of congenital malformations was first reported in the 1980s when Lancaster found a higher incidence of neural tube defects and cardiovascular defects in babies born by ART.[2] Since then, authors have reported inconsistent causal associations between ART and the risk of birth defects. Initial studies by Wright et al[3] and Ludwig et al[4] reported an inconclusive link between the two.[3,4] Studies from Australia and Sweden reveal a higher incidence of congenital malformation in In-Vitro Fertilization (IVF) pregnancies compared with naturally conceived pregnancies.[5,6] A recent systematic review and meta-analysis involving 45 cohort studies also showed that ART babies have a 32% higher risk of birth defects compared with naturally conceived infants.[7]

In contrast, Davies et al concluded that the unadjusted odds ratio for any birth defect in ART pregnancies compared with natural pregnancies was 1.47 (95% confidence intervals [CI] 1.16-1.41); after adjustment of parental factors this risk was no longer significant in IVF pregnancies but remained increased for Intra Cytoplasmic Sperm Injection (ICSI).[8] Simpson in his review observed that although ART is associated with a 30% increase in birth defects, sub-fertile couples achieving pregnancy without ART also show a 20% increase in birth defects.[9]

Birth defects are a global problem, but their impact is particularly severe in economically developing countries where more than 94% of the births with serious birth defects and 95% of the deaths of these children occur.[10] There is a paucity of data especially from these countries where there is a lack of a structured database to monitor the outcomes of pregnancy following ART in economically developing countries such as India. In addition, globally, there is lack of data comparing the congenital birth defect in IVF cycles separately for autologous and donor oocytes. In recent years, the use of donor oocyte in ART is increasing due to poor oocyte quality, decreased ovarian reserve and improved surveillance for the detection of maternally carried genetic defects in pre-implantation stage embryos. This stresses the need to study increased risk, if any, with the congenital malformation resulting from donor oocytes. This is the first study addressing the prevalence of birth defects with donor oocytes, comparing it with the autologous oocytes in IVF-ICSI cycles. We also compared the above result with natural pregnancies in a national as well as global populations.

Key message

This is the first study reporting the birth defects in pregnancies following IVF-ICSI with donor and autologous oocytes and comparing them with those resulting from natural births in India. The overall birth defect rates were similar compared with natural births, and differences in cycles resulting from autologous and donor oocytes were not significant.

2 | MATERIAL AND METHODS

This retrospective observational study was conducted at an Indian infertility center (Nova IVI Fertility, Ahmedabad, India). To detect a statistical difference between the two groups with minimum detectable effect, we would require a very large sample size. Nonetheless, with the aim of looking at even the minimal changes in neonatal outcome derived from autologous and donor oocytes, we included all the patients who had a positive pregnancy test after ET following IVF-ICSI carried out between 1 January 2014 and 31 December 2016. Fresh ET was done on day 3 or 5 post egg retrieval and frozen ETs were done after thawing of a day 3 or 5 embryo. All the patients were provided standard antenatal care at a well-equipped obstetric center by the obstetrician of their choice, after confirmation of pregnancy.

2.1 | Eligibility criteria

All women who conceived following an ET (fresh or thawed) during the study period were included in this study. The embryos in the study were derived from ICSI using autologous or donor oocytes. Women were offered treatment with donor oocytes in cases of advanced maternal age, poor ovarian reserve, poor response to IVF with autologous oocytes and premature ovarian failure.

2.2 | Data collection

Each obstetrician was provided with a standard proforma for pregnancy surveillance and to record the pregnancy outcome – both maternal and perinatal. The proforma was handed over to the woman at the time of obstetric referral and the same document was communicated to the respective obstetrician by telephone. They were requested to note the antenatal records on the form and send them to our center within a month of abortion, ectopic pregnancy or delivery. In cases where the obstetrician could not be contacted, the details regarding pregnancy outcome were obtained from the subjects personally by telephone. Relevant antenatal history in the antenatal period such as drug history and exposure to teratogens was also sought; only women with no significant contributory cause of birth defects were included. Details of antenatal complications, mode of delivery, perinatal outcome and birth details were recorded.

If a congenital anomaly was detected on the sonogram, it was noted specifically and followed subsequently. The outcome of pregnancy in fetuses with birth defects was noted at termination of pregnancy, birth (live or still birth) or post-delivery follow-up till the neonatal period.

2.3 | Outcomes assessed

The study assessed the incidence of structural birth defects in pregnancies of women who conceived following IVF-ICSI using autologous and donor oocytes and compared it with the incidence of birth defects following natural conception. These structural birth defects in the study population were classified system-wise according to the European Surveillance of Congenital Anomalies: EUROCAT (European Concerted Action on Congenital Anomalies and Twins) classification of birth defects.[11] Where a major congenital malformation was detected before 20 weeks, medical termination of pregnancy was offered to the patient. In non-lethal birth defects compatible with life, pregnancy was continued till term and the perinatal outcome was noted. Undiagnosed birth defects during antenatal period that were detected at birth of the baby were also reported. These were picked up by the obstetrician after birth and confirmed by a pediatrician.

The system-wise incidences of these birth defects were compared with the rates in natural pregnancies. Individual incidences in cycles resulting from autologous and donor oocytes were also analysed for its statistical significance.

2.4 | Statistical analyses

The prevalence of birth defects between different study groups (autologous oocytes and donor oocytes; IVF-ICSI pregnancies and natural births) was compared by calculating the relative risks/risk ratios using two-tailed *P* values; this enabled us to establish varying levels of incidence of events when compared within different study groups. It is understood that a risk ratio = 1 implies that the incidences are almost the same in both groups and an risk ratio of <1 or >1 would imply a lesser or higher risk of a particular event in the case group as compared with the control group. The significance between the groups was also analysed by Fisher's exact *t* test using R software (https://www.r-project.org/).

2.5 | Ethical approval

Prior ethical approval was sought from the Institutional Ethical Committee (KB Institute Ethics Committee) dated 10 March 18 (no. KBIPER/2018/104).

3 | RESULTS

During the study period spanning 3 years (1 January 2014 to 31 December 2016), there were 2444 births, comprising 2350 live and 94 still births. Of these 2444 births, 1743 resulted from IVF-ICSI cycles with autologous oocytes and 701 cycles using donor oocytes. There were 29 pregnancies with birth defects: 20 from ICSI with autologous oocytes and 9 from donor oocytes. Of these 29 pregnancies, 24 were singleton and 5 were in a coexisting twin. All the pregnancies were followed up. Table 1 depicts the incidence of the birth defects classified system-wise in both autologous and donor oocyte cycles, and Table 2 compares it with the standard reported rates in the literature, both worldwide and from India. The overall prevalence of birth defects was 29/2444, or 118.6/10 000 births, and the most common structural congenital birth defect reported was cardiac malformation (32.7/10 000 births) followed by genitourinary malformation (28.6/10 000 births). Among IVF-ICSI cycles with autologous oocytes, the prevalence of gastrointestinal, cardiac and genitourinary defects was similar (5/1743, or 28.6/10 000 births each). In cycles with donor oocytes the most common malformation was cardiac (3/701, or 42.7/10 000 births). The details of fetal malformations in each group (autologous and donor oocytes) are detailed in Table S1. Overall, there were 2 women with fetal genetic anomalies: cystic hygroma (from autologous oocytes) and hypoplastic nasal bone (from donor oocytes group) on a sonogram with a positive aneuploidy screening test: both women underwent termination of pregnancy in the second trimester. There was one metabolic anomaly (from the donor oocyte group): congenital hypothyroidism. One woman (from autologous group) had a fetus with multiple anomalies: Cardiovascular, neural and limb defect.

Among the pregnancies with birth defects, 8 were terminated in the second trimester, the defects being major malformations. Seven babies underwent surgery: 3 for gastrointestinal malformations, 1 for mild hydrocephalus and 3 for cardiovascular defects.

The mean maternal age in autologous oocyte group was 31.6 years; in donor group the mean age of the donor was 26.7 years and that of the recipient was 36.3 years. The differences between the mean maternal age in the autologous and donor oocytes were statistically significant ($P < 0.001$).

In the subgroup analysis, the differences in prevalence of a specific congenital birth defect in either autologous or donor oocyte

group was not statistically significant (Table 2; *P* values in each subgroup, $P > 0.05$). Although the autologous oocyte group had a higher trend of gastrointestinal malformations (28.6/10 000), there was a lower rate of cardiovascular defects (28.6/10 000 vs 42.7/10 000 births) and central nervous system malformations (5.7/10 000 births vs 14.2/10 000 births), though these differences were statistically insignificant.

Table 2 shows the system-wise prevalence of birth defects in the two groups (autologous vs donor) and compares the overall rates with national and global rates in standard birth defects rates for India from published data – National Neonatal and Perinatal Database (NNPD), World Health Organization (WHO)-South East Asia Regional Office (SEARO) and EUROCAT for global incidences.[11-13] The prevalence of gastrointestinal and genitourinary malformations was not significantly higher than both national and global incidences in this published data. The incidence of cardiovascular defects was significantly higher in this study compared with national incidence (32.7/10 000 vs 12.7/10 000; $P = 0.005$) but lower compared with global results (77.57/10 000; $P = 0.06$). Similarly, the incidence of central nervous system malformations was also much lower in this study (8.1/10 000) compared with both national (20.23/10 000; $P = 0.005$) and global (25.97/10 000; $P = 0.16$) incidences.

4 | DISCUSSION

Congenital anomaly birth rate is defined in the International Committee Monitoring Assisted Reproductive Technologies (ICMART) 2017 glossary as the number of births exhibiting signs of birth anomalies per 10 000 births.[14] The EUROCAT estimates birth defects with different denominators: Live births, total births and total births with added termination of pregnancies due to fetal anomalies.[11] In the present study, birth defect prevalence rates were calculated per 10 000 births. The March of Dimes report estimated that India has one of the largest number of infants born with birth defects globally (64.3/1000 live births)[10] but with improvements in health care and intensive care facilities, many infants with birth defects have better survival rates. Indian data on birth defects reveal varying results, because of the geographic variation in birth defects, varying standards of data collection in each study, case definition and other methodological issues. The reported prevalence of birth defects provided by the Birth Defects Registry of India (BDRI) in 2010 was 84.2/10 000, much lower than the estimated prevalence of at least 2% in 2001.[15]

The implication of IVF-ICSI using autologous or donor oocytes on birth defect rate has not been exclusively reviewed in the literature. With the increasing application of IVF-ICSI cycles for a successful pregnancy outcome (especially using donor oocytes), the controversial association between ART cycles and birth defects needs to be addressed separately. A few authors have noted a similar birth defect rate in pregnancies resulting from donor oocytes and in natural conceptions[16,17] but these have not been compared with those from autologous oocytes. A recent study from Sweden analysed the neonatal outcome in births resulting from donor and autologous oocytes with birth defects as one of the outcomes assessed. Though the birth defect rates were similar in these groups in donor oocytes (4/72) and autologous oocytes (4/60; 95% CI 0.20-0.34), the numbers were too low to be significant.[18] Another study from our group found similar rates of birth defects in pregnancies following fresh ET using autologous (1.39%) vs donor oocytes (1.32%) as a perinatal outcome over a 1-year period, but again, the number of cases (4 each) were less in each subgroup.[19] This is probably the first study to compare the prevalence rate of birth defects system-wise in the two groups as a follow-up analysis over a 3-year period.

This retrospective data analysis of 2444 births resulting from IVF-ICSI during a 3-year span revealed a similar congenital anomaly rate in IVF-ICSI using autologous and donor oocytes. Although there was a trend towards a higher prevalence of gastrointestinal birth defects and a a slightly lower prevalence of cardiovascular and central nervous system birth defects in the autologous oocyte group than in the donor group, these were not statistically significant. Additionally, the birth defect rate noted in IVF-ICSI pregnancies was similar to natural conceptions in India.

Overall, there was no statistical difference in the birth defect rate in births resulting from IVF-ICSI using autologous or donor oocytes. However, we report five cases of gastrointestinal malformation in the group with oocyte donors and none in the autologous group, where the mean maternal age was lower in the latter group (31.6 years) compared with the donor oocyte group (36.3 years); the mean age of the ooctye donor was 26.7 years. Thus, the observed difference may be explained by the epigenetic effect due to

TABLE 1 Prevalence of congenital birth defects between IVF-ICSI cycles with autologous and donor oocytes

	Autologous oocytes (n)	Donor oocytes (n)	Total (n)
Gastrointestinal malformation	5	0	5
Genitourinary malformation	5	2	7
Cardiovascular system malformation	5	3	8
Central nervous system malformation	1	1	2
Others	4	3	7
Total	20	9	29

TABLE 2 Comparison of birth defects incidence in study groups (autologous and donor oocytes), classified system-wise with the reference to values in normal population

Type of malformation	Prevalence per 10 000 births (number of malformations / total number of births in the group) × 10 000				Comparative reference (prevalence per 10 000 births)				
	Total (n = 2444)	Autologous (n = 1743)	Donor (n = 701)	*P* value	Indian: NNPD (Ref[12]) (2002-2003)	IVF-ICSI vs National rates	WHO SEARO (Ref[13])	EUROCAT (Ref[11]) data (2011-2015)	IVF-ICSI vs global rates
Gastrointestinal malformations	20.5 (5/2444)	28.6 (5/1743)	0.33	0.33[a]	18.6	*P* = 0.19; RR: 1.13; CI: 0.2-1.3	38.37	17.52	*P* = 0.79; RR: 1.13; CI: 0.4-3.05
Genitourinary malformations	28.6 (7/2444)	28.6 (5/1743)	28.5 (2/701)	0.996	24.7	*P* = 0.54; RR: 1.3; CI: 0.55-3.04	21.58	56.43	*P* = 0.12; RR: 0.54; CI: 0.24-1.18
Cardiovascular malformations	32.7 (8/2444)	28.6 (5/1743)	42.7 (3/701)	0.58	49.09	*P* = 0.03; RR: 2.5; CI: 1.04-6.06	12.7	66.57	*P* = 0.06; RR: 0.49; CI: 0.23-1.03
Central Nervous System malformations	8.1 (2/2444)	5.7 (1/1743)	14.2 (1/701)	0.52	20.23	*P* = 0.005; RR: 0.14; CI: 0.03-0.55	60.18	25.97	*P* = 0.16; RR: 0.36; CI: 0.08-1.5
Total incidence (including others)	118.6 (29/2444)	114.7 (20/1743)	128.38 (9/701)	0.91	163.84	*P* = 0.12; RR: 0.6; CI: 0.31-1.17	212	257.06	*P* = 0.03; RR: 0.49 CI: 0.25-0.96

CI, confidence interval; RR, relative risk.
[a]Fisher's exact test.

the higher maternal age in women opting for donor oocyte cycles. Additional coexisting factors such as diabetes, obesity, prolonged infertility and lifestyle factors can pose an additional risk for causing birth defects in women undergoing IVF-ICSI with donor oocytes and may nullify the advantage of using younger eggs. These factors influence the micro-environment of the developing embryo and may alter the gene expressions and epigenetic reprogramming, leading to DNA modifications. This possible confounding variable and an additional risk for birth defects needs to be explored in an animal model to achieve a better understanding of the confounding effects of coexisting infertility and maternal age.

India, with its recent economic development, has led to improved health care, and IVF is one of the fast developing fields of medical care. However, there is lack of data from the Indian subcontinent on congenital anomalies resulting from IVF-ICSI cycles. Thus, it is important to undertake such studies to understand the risk, if any, in children born of IVF-ICSI. This will not only build confidence in the treating doctors, but also will encourage the general public to accept IVF treatment without hesitation, as a large proportion of those attending clinics are from the upper economic class.

As a secondary outcome, the birth defect rates were compared with those in natural conceptions in the Indian population. This study shows a congenital anomaly rate of 118.6/10 000 births from IVF-ICSI in Indian population, still lower than those reported in the general population by NNPD (163.84/10 000; *P* = 0.12) and the WHO-SEARO report (212/10 000; *P* = 0.47).[13] These results are also significantly lower than those reported in EUROCAT (257.06/10 000; *P* = 0.03). However, globally, there are contradicting reports showing a higher risk of birth defect following ART (odds ratio [OR] 1.47, 95% CI 1.16-1.41; adjusted OR 1.28). Similarly, a recent review of the meta-analyses of studies reporting the incidence of birth defects after ART noted a 30% increase in birth defects in ART pregnancies (OR 1.3).[7] However, neither study ruled out residual confounding, and both attributed these higher rates to the biological perturbations that caused infertility rather than to ART alone. This study evaluates the risk of birth defects in a cross-section of the general population seeking IVF-ICSI using autologous and donor oocytes. Since there are no major data from this section of the population, the results were compared with natural conception in the general population.

The most common congenital anomaly in the present study was cardiovascular (32.7/10 000), followed by genitourinary (28.6/10 000). Although ICSI has been found to have a higher rate of genitourinary birth defects in resulting pregnancies, in this study the rates were comparable to the general population. The higher frequency of cardiovascular defects (32.7/10 000) in this study was consistent with the higher rates reported earlier[20,21] but were lower compared with EUROCAT (66.57/10 000) and NNPD estimates (49.09/10 000), and higher compared with the general population risk cited by the WHO-SEARO report (12.7/10 000). These differences could be due to variation in the method of birth defect estimation in the above studies. Also, with better antenatal surveillance and sonological advancements, the frequency of

detection of cardiac anomalies is higher in the antenatal period, which may explain the higher rates in the study population, as IVF pregnancies are high-risk pregnancies and are monitored more closely. Similarly, the risk of neural tube defects (8.1/10 000) and limb defects (12.2/10 000) were significantly much lower than in the general population (WHO-SEARO: 60.18/10 000; $P = 0.005$; EUROCAT 25.97/10 000; $P = 0.16$). The risk of gastrointestinal birth defects (20.5/10 000) was lower compared with national estimates (38.37/10 000) but were slightly higher compared with global rates (17.5/10 000; $P = 0.79$).

It is a misconception that ART pregnancies have higher birth defect rates compared with natural conceptions. In fact, such pregnancies are high risk and precious, and therefore have better antenatal surveillance. Therefore, the chances of detection of birth defects in the antenatal period is higher when compared with general population.

To achieve a power of 80%, a sample size of 163 940 and 81 900 is required in Autologous and donor oocyte groups, respectively, for the observed level of incidents in this study. This may take several years to carry out. However, studies with meta-analysis will help in reducing the time.

5 | CONCLUSION

This study involved 3-year data on children with a number of birth defects (29/2444 births), which is still too low to achieve significant statistical difference. Additionally, the babies were followed up only till the neonatal period for birth defects; any birth defects detected later may have been missed. The major reason for the lack of databases in developing countries is the absence of dedicated birth registries for follow up. Therefore, we limited this study to early neonatal follow up of the babies. Although the study group is small number in number, some results in the study are close to significance. A larger number of cases in the study group might provide a better understanding of the risk in different groups. Despite these limitations, this is the first study to analyze the risk of birth defects from ART in the Indian population with robust data; the study also compares the risks of birth defects in babies resulting from autologous and donor oocytes. Proper ART registries and long-term follow-up data may help in better preconceptional ART counseling and prognostication of the risk of birth defects after IVF.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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