Perinatal outcomes among children born by assisted reproductive techniques—a hospital-based case control study

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ABSTRACT

BACKGROUND

Widespread use of assisted reproductive techniques (ART) has raised major concern about the outcome of resulting pregnancies, as well as about the health of the newborn children. The ART conceived pregnancies have an increased risk for prematurity and low birth weight (LBW). The risk of congenital malformations among children conceived via ART is contemplated to be high. The present case control study was conducted with an aim of analysing perinatal outcomes of children born by ART in the Indian context.

METHOD

The case control study was conducted in the Army Hospital (Research and Referral), New Delhi. It included 82 cases and 164 controls. The data was collected on maternal and newborn characteristics among cases and controls. Perinatal outcomes were compared between ART conceived and spontaneously pregnant women in terms of birth weight, preterm, multiple pregnancies, and neonatal complications.

RESULTS

Significant difference was observed in terms of the preterm delivery, birth weight, neonatal complications between the cases and the controls. The adjusted odds ratio (OR) was 21.6 (95% confidence interval [CI] 4.3, 112.9) for preterm delivery; 6.0 (95% CI 1.1, 43.8) for multiple pregnancy and 3.2 (95% CI 1.5, 7.0) for caesarean section. The risk of LBW and neonatal complications was heavily confounded by preterm delivery and multiple pregnancies, the adjusted OR being 0.9 and 1.0, respectively.

CONCLUSION

Increased risk of preterm delivery, multiple pregnancies and caesarean section was associated with ART. The LBW was confounded by preterm delivery and multiple pregnancies.

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Key Words: assisted reproductive techniques; odds ratio; perinatal outcomes

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INTRODUCTION

Assisted reproductive techniques (ART) have rapidly evolved over the past 20 years,^{1,2} with infertility affecting approximately 13–14% of the reproductive-aged couples.³ Assisted reproductive techniques has helped couples all over the world and rising trends have been reported in applications of ART globally.⁴ Several novel ART have been introduced over this relatively short span of time. During the initial phase of ART applications, the stress was on successful conception but now it has rightly shifted to whether the children born by these techniques are normal and healthy.² In the developed countries, various methods of ART such as in vitro fertilisation (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT) and intracytoplasmic sperm injection (ICSI) are now extensively used.¹ Currently, ARTs are being widely employed in India.⁴

Various studies^{5,6} have reported that the children born to women who conceived with ART, were premature and had low birth weight (LBW). There has been an increased incidence of congenital malformations.^{7,8} There is a higher propensity for multiple pregnancies in ART.⁹ There have not been many studies done in the Indian context where the socio-economic background is very different, and the reproductive morbidity among women is high. The occurrence of sexually transmitted diseases, genital tuberculosis, pelvic inflammatory diseases, and abortions, which are often directly or indirectly associated with infertility, are quite frequent among Indian women, especially those belonging to low socio-economic strata.^{10,11}

The present study was conducted to assess the association of applications of ART with various perinatal outcomes. We present occurrence of various perinatal outcomes among women who conceived with ART at the Army Hospital (Research and Referral), New Delhi, an apex hospital in the Armed Forces with a highly specialised ART centre.

MATERIALS AND METHOD

The present study is a case control study conducted in Army Hospital (Research and Referral) and Base Hospital, both located in New Delhi. Army Hospital (Research and Referral) is a super specialty hospital with a specialised ART centre for infertility treatment, and the Base Hospital is a 300 bedded

general hospital where women with spontaneous pregnancy are provided essential and emergency obstetric care during child bearing. In the Army Hospital (Research and Referral), the patient is taken care of in the infertility centre till the end of first trimester. Following this, for the next two trimesters antenatal care is provided by the Department of Obstetrics and Gynaecology, Army Hospital (Research and Referral) wherein the pregnant women are duly monitored for normal foetal growth and pregnancy associated complications, especially pregnancy-induced hypertension, gestational diabetes mellitus, and other complications during pregnancy as these conditions have been found to be commonly associated with these techniques.¹¹

The study included 82 cases and 164 controls. Cases were the newborn babies born to the women who received treatment for infertility and conceived with ART in Army Hospital (Research and Referral). The newborn babies born to spontaneously pregnant women were taken as controls. All the newborn children born (cases) to the ART conceived women between December 2009 and March 2010 in Army Hospital (Research and Referral) were included in the study. The controls were selected randomly among the newborn children of spontaneously pregnant women in Base Hospital, Delhi Cantt. during the corresponding period. The sample size was determined by using Epiinfo (Version 6.0), with $\alpha=0.05$ and β error as 0.20 to detect a minimum odds ratio of 3. The sample size had power >80% to detect the significant difference in perinatal outcomes with 95% confidence interval (CI) ($\alpha=0.05$).

The data was collected from the records of the Department of Obstetrics and Gynaecology, and Department of Paediatrics at both hospitals. The statistical analysis was conducted using SPSS (16th version). Chi-square and *t*-test were performed to test the significance in bivariate analysis. Simple logistic regression was carried out to estimate odds ratio (OR) and CI. Multivariable logistic regression was performed to evaluate the effect of confounding and calculate adjusted OR.

RESULTS

A comparison of characteristics of cases and controls was done to assess whether the cases and controls were comparable (Table 1). The average age of the women who conceived with ART, 29.34 (SD $\pm$ 3.36) years, was significantly higher ($P<0.05$) than those who conceived spontaneously. Over 86% of ART conceived women were of age >25 years. The women who received ART had experienced significantly higher occurrence of abortions prior to current pregnancy, the mean number of abortions being 0.49 $\pm$ 0.76, as compared to 0.24 $\pm$ 0.57 among spontaneously pregnant women ($P<0.001$).

The cases had a significantly lower mean birth weight as compared to born to spontaneously pregnant women ($P<0.001$). Nearly, half the newborn children (45.6%) among cases had a LBW as compared to newborn children among spontaneously pregnant women. This difference was statistically significant. Most of the women, 58.5%, who conceived

Table 1 Comparison of characteristics of assisted reproductive techniques pregnant (cases) and spontaneously pregnant women (controls) and newborn babies.

Characteristics	Cases (N=82)	Controls (N=164)	P value
Women			
Mean age of women (yr)	29.34 $\pm$ 3.36	25.82 $\pm$ 3.37	<0.05
Age distribution of women (%)			
<25 yr	13.4	48.1	<0.05
>25 yr	86.6	51.9	
Gravida (mean $\pm$ SD)	1.54 $\pm$ 0.85	1.91 $\pm$ 0.86	<0.001
Abortions (mean $\pm$ SD)	0.49 $\pm$ 0.76	0.24 $\pm$ 0.57	<0.001
Newborn			
Mean birth weight	2.35 $\pm$ 0.06	3.10 $\pm$ 0.03	<0.05
Percent LBW (%)	45.6	3.6	<0.001
Preterm (%)	58.5	2.5	<0.000
Neonatal complications (%)	15.9	1.2	<0.001
Twins/multiple pregnancy (%)	40.2	0	<0.000

LBW: low birth weight, SD: standard deviation.

with ART, delivered preterm newborn baby. The proportion of preterm babies among them was significantly high as compared to the newborns delivered by the spontaneously pregnant women ($P<0.000$). Occurrence of twin pregnancies was common among women conceived with ART. Almost 40% of them delivered twins, which was statistically significant ($P<0.000$). Furthermore, incidence of complications was significantly high among the newborns delivered by the ART pregnant women ($P<0.001$). Table 2 presents the risk of various perinatal outcomes among cases and controls using simple and multivariable logistic regression analysis.

Simple logistic regression showed that the risk of preterm birth was >42 times among the ART conceived women than spontaneously pregnant women (OR 41.9, 95% CI 15.5, 113.1). Analysis showed that ART conceived women had almost 22 times higher risk of giving birth to babies with LBW (OR 22.3, 95% CI 8.8, 56.5). The propensity to multiple pregnancies was very high among the ART conceived women, as many as 54 times as compared to spontaneously pregnant women.

The risk of complications among newborn babies born to ART conceived women were >15 times as compared to babies born to spontaneously conceived women (OR 15.1, 95% CI 3.31–66.0).

The analysis also showed that most of the ART conceived women required surgical interventions. The caesarean section was almost 10 times higher among these women as compared to spontaneously pregnant women (OR 9.9, 95% CI 5.2, 18.7).

Table 2 Simple logistic regression and multivariable logistic regression analysis.

Birth outcomes	Simple logistic regression		Multivariable logistic regression	
	OR	95% CI	OR	95% CI
Low birth weight	22.3	8.8, 56.5	0.9	0.2, 6.2
Preterm	41.9	15.5, 113.1	21.6	4.3, 112.9
Twins/multiple pregnancy	53.8	12.4, 232.6	6.0	1.1, 43.8
LSCS/assisted reproduction	9.9	5.2, 18.7	3.2	1.5, 7.0
Neonatal complications	15.1	3.3, 66.0	1.0	0.07, 12.5
Maternal age	5.9	2.9, 12.1	4.3	1.7, 11.1

CI: confidence interval, LSCS: lower segment caesarean section, OR: odds ratio.

The results of multivariable logistic regression analysis have also been presented along with the simple logistic regression analysis. The multivariable analysis showed that the LBW was confounded by preterm and multiple pregnancies. The LBW was reduced to a null value (OR 0.9, 95% CI 0.2, 6.2), when preterm variable was introduced in the model. The risk of the preterm babies (OR 21.6, 95% CI 4.3, 112.9) and multiple pregnancies (OR 6.0, 95% CI 1.10, 43.8), though reduced in the presence of other variables, but remained independent of all of them. The association between lower segment caesarean section (LSCS)/assisted reproduction and ART conceived women, though reduced in its magnitude, but remained high and independent of other factors.

Interestingly, the risk of neonatal complications became insignificant in the presence of other factors, specially, preterm, multiple pregnancies, and LSCS.

DISCUSSION

There has been an increasing trend of use of ART globally, including India as an ever increasing number of infertile couples are seeking treatment.^{1,4} While ART has helped infertile couples, these techniques have been associated with adverse pregnancy outcomes. There was an increased risk of LBW, preterm babies and multiple pregnancies. Our study corroborated the findings of an earlier study carried out in our hospital which showed an excess prevalence of multiple births, LBW, and preterm babies among ART conceived women.¹¹ However, that study was descriptive in nature, and did not use comparison group. Our study in turn is perhaps the first to use a case control study design to assess the risk of adverse birth outcomes and factors associated with them in the Indian context.

The results of our study were consistent with the findings of other studies.^{2,6} Our study was reliable and had reasonable internal validity. The power of the sample was >80% to detect

statistically significant difference in perinatal outcomes between ART conceived and spontaneously pregnant women. However, the possibility of selection bias cannot be ruled out as the cases and controls were selected from different sources. The cases were selected from Army Hospital (Research and Referral), which is an apex referral centre, and controls (born to spontaneously pregnant women) from the Base Hospital, Delhi Cantt. Possibility of selection bias due to referral might exist, however, the strength of association (OR) between ART and various perinatal outcomes was high and significant. Further, since all the patients were from army families, we assumed that the selection bias due to differential source of cases and controls would be minimal. The confounding effect of the social-cultural factors would have been minimal as all the families came from the similar background.

In our study, the risk of LBW became non-significant when adjusted for preterm births and multiple pregnancies. In the presence of the latter two variables in the model, the risk of LBW was reduced to a null value, thus providing an evidence of confounding due to these factors. The study showed a highly significant risk of preterm births and multiple pregnancies among ART conceived women. The increased risk of preterm baby was significant and independent of all other factors including LBW, multiple pregnancies and maternal age.

The pregnancy in ART conceived women being precious; they were very meticulously monitored as per protocols from 32 weeks onwards and maintained on progesterone. They were hospitalised at 36 weeks of gestation. Many of them were delivered as soon as they reach 36 weeks of gestational age and even before. Since multiple pregnancy was common among ART conceived women, the risk of preterm birth was increased. It has been reported that the preterm delivery rates were 10% among singletons, however, the rates for twins were nearly 50%, and those for triplets were >95%.¹² The women were delivered if there was onset of labour and risk of neonatal complications. As a result, significantly higher number of babies was preterm with greater tendency for LBW. Apart from this, LBW could be also due to multiple pregnancies and maternal malnutrition among pregnant women due to lower educational and socio-economic status.

The babies born by assisted reproductive technologies showed a 15 times higher risk of neonatal intensive care unit (NICU) admission. They were admitted mostly for supportive care for initiation of feeding, a few developed complications like neonatal jaundice, neonatal sepsis, and difficult respiration. There was only one baby among 82 cases with multiple congenital malformations who did not survive even after resuscitation. Hansen et al reported a 30–40% significantly increased risk of birth defects among children born to ART conceived women in a meta-analysis of 25 studies.⁶ Increase in risk of epigenetic inheritance of congenital malformations and chromosomal abnormalities has been reported among children born to ART conceived women.^{13,7} In addition, maternal health may also be affected with ART conceived women. Our study has revealed a 10 times risk of LSCS among the ART pregnant women, most of which were elective.

High-risk of vaginal bleeding throughout pregnancy, threatened preterm delivery and intrahepatic cholestasis of pregnancy has been reported among ART pregnant women.¹⁰ The pregnancy related complications with ART might be due to maternal factors related to infertility and high incidence of multiple pregnancies.

Assisted reproductive techniques has emerged as an important technique, especially for the women who have primary infertility. In our study, 80.48% patients had primary infertility and 19.51% secondary infertility. In countries like India, application of ART is expected to rise due to technological advances and increased access to infertility treatment. The high-risk of preterm births with ART is a cause of public health concern, as preterm delivery accounted for about 70% perinatal mortality, though we did not observe a single still birth in our study.⁵ The preterm born survivors are at increased risk of growth and development problems. The rise in preterm births and long-term implications on growth and development and psych-behavioural health has raised concerns with potential widespread use of ART.¹³ As is common in ART, there were cases of triplets and quadruplets reported in many studies.^{6–8,11} A further research is wanted to refine ART to improve birth outcomes; especially reducing risk of LBW babies and multiple pregnancies. At our centre, the infertile women were treated with embryo reduction techniques, thus reducing the multiple pregnancies just to twins. A prospective study is warranted that follows a cohort of the ART born children during infancy through early childhood to assess the ART related morbidity and mental development needs of such children.

Intellectual Contributions of Authors

Study concept: Capt Preeti Gupta, Capt Neelabh Nayan

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CONFLICTS OF INTEREST

None identified.

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