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Original Research Article

Comparison of maternal and neonatal outcome of IVF/ICSI conceived pregnancies with spontaneous conceived pregnancies

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ABSTRACT

Background: Conception by IVF has been associated with an increased incidence of several obstetrical and perinatal complications. IVF is associated with increased complications like OHSS (Ovarian Hyper Stimulation Syndrome), multiple pregnancies and thromboembolism, ectopic pregnancy, congenital malformations, and small for gestational age, low birth weight etc. This study is done to evaluate and compare the obstetric and perinatal complications between assisted reproduction and spontaneous conception. The objective of the present study was to evaluate and compare the maternal and neonatal outcome of IVF/ICSI conceived pregnancies with spontaneous conceived pregnancies.

Methods: In this study 62 patients conceived with IVF/ICSI were taken as cases and 62 patients conceived spontaneously were taken as controls. The categorical data was analyzed using chi square test and results expressed by p value.

Results: The incidence of multiple pregnancies among IVF/ICSI group is 33.8% and 1.6% in controls. IVF/ICSI conception when compared to spontaneous conception is associated with increased incidence of miscarriage (18% versus 1.6%), first trimester bleeding (18% versus 1.6%), cervical insufficiency (22.5% versus 0), PROM (11.3% versus 1.6%), preterm birth (33.8% versus 14.5%), caesarean section rates (71% vs 53%), low birth weight babies (44% vs 10.7%) and NICU admissions(33.3% vs 10.7%). The male: female ratio is higher in IVF/ICSI group.

Conclusions: IVF/ICSI conceptions are associated with a significantly higher incidence of multiple pregnancies, miscarriage, prematurity, increased caesarean section rates, and increased male: female ratio.

Keywords: IVF/ICSI, Obstetric and neonatal outcome, Spontaneous conception

INTRODUCTION

Simple assisted reproduction includes induction of ovulation, follicular scanning, and intrauterine insemination. If multiple cycles fail, if there is a tubal factor, or if there is a male factor etc, the patients are then recommended in vitro fertilisation and embryo transfer popularly referred to as IVF- ET. It is hence an important form of treatment for infertility when other methods of assisted reproductive techniques have failed. Conception by IVF has been associated with an increased incidence

of several obstetrical and perinatal complications. Traditionally, IVF outcome has been expressed in terms of biochemical, clinical pregnancies or total live births. IVF is also associated with complications specific to itself like OHSS (ovarian hyperstimulation syndrome), multiple pregnancies and thromboembolic complications. There are reports to suggest an increased incidence of ectopic pregnancy, miscarriage, congenital malformations, and small for gestational age, low birth weight, preterm birth, stillbirth, perinatal death and increased rates of caesarean section.¹⁻³ The precise

reasons for this increase in adverse outcomes are not clear, but potential reasons include: maternal and paternal characteristics, underlying medical conditions associated with subfertility and infertility, sperm factors, the use of fertility medications, laboratory conditions during embryo culture, culture medium, cryopreservation and thawing, prenatal genetic diagnosis (if performed), differences in obstetrical management, increased proportion of multiple gestations and vanishing twins, or a combination of these factors. The effects of advanced maternal age also should not be underestimated, since many women who undergo IVF are older and older women are more likely to have relatively more pregnancy complications.⁴

With a view to assess unbiasedly, the truth behind association between perinatal complications and assisted reproduction, the present study is being undertaken. In this study conducted at Manipal Hospital, Bangalore, the association between maternal and foetal outcomes in pregnancies following IVF/ICSI conceptions had been evaluated and compared with spontaneous conceptions.

METHODS

The present study is a prospective case control study conducted in the Department of Obstetrics and Gynaecology, Manipal Hospital, Bangalore between October 2013 and October 2014. In this study 62 patients conceived by IVF/ICSI as cases and 62 patients conceived spontaneously as controls were included. Permission for the study was obtained from the College authorities prior to commencement.

Exclusion criteria

- Women who have conceived with other forms of assisted reproductive techniques, with history of consanguineous marriage and patients with co-existing medical disorders (cardiac disease, pregestational diabetes, hypertension) were excluded from the study.

Patients were enrolled after taking the written informed consent. The demographic data such as age, occupation etc were obtained and detailed obstetrical, menstrual, medical, past history and also husband brief history entered in the profroma. These cases were followed up throughout the course of pregnancy, all complications like miscarriage, GDM, PIH, mode of delivery and neonatal complications were noted.

Statistical analysis

Observational and inferential statistical analysis has been carried out in the present study. The data obtained entered into Microsoft Excel worksheet and then analysed using chi square test and results expressed by p value. Statistical significance was defined as a p value of less than or equal to 0.05.

RESULTS

In the present study majority of women in both groups were in age group of 25-34 years. In IVF/ICSI pregnancies around 29% of women are above 35 years of age and 6.5% in control group Figure 1.

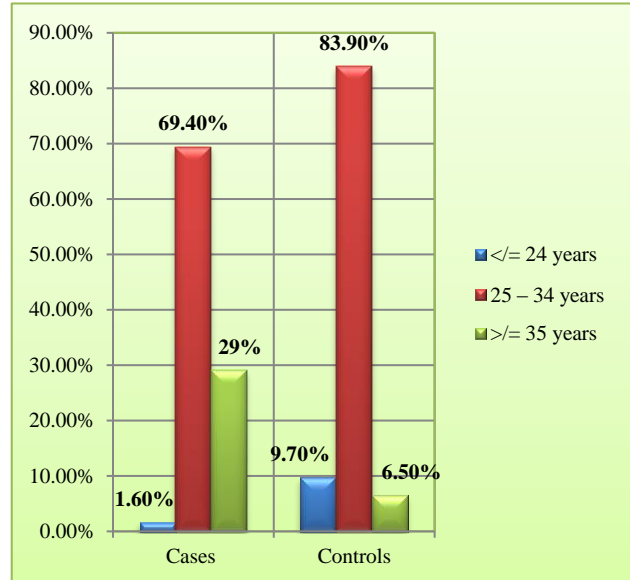


Figure 1: Comparison of age of patients.

In IVF/ICSI group 71% of women had primary infertility and 29% secondary infertility. 40.3% women in IVF/ICSI group had irregular cycles compared to 5% women in the control group Figure 2.

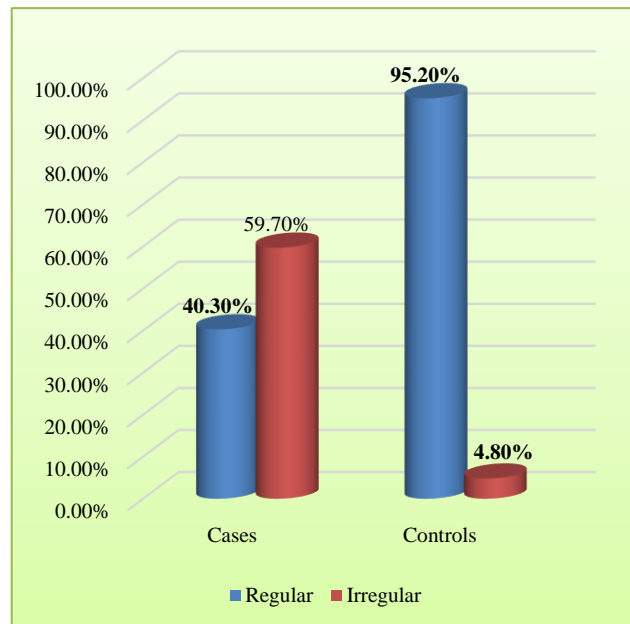


Figure 2 Comparison of menstrual cycles.

29% of patients among IVF/ICSI group and 18% in controls were hypothyroid. Five patients among IVF

group had of tuberculosis, 2 of them were treated cases of pulmonary tuberculosis and 3 had endometrial tuberculosis. 2 patients in each group had epilepsy. Polycystic ovarian syndrome (PCOS) is present in 46.7% of cases and 6% of controls (p value-0.04). Amongst the cases 89% had increased BMI compared to 61% among controls. Among the indications for IVF/ICSI, 40.3% of patients had male factor, 32.2% had ovarian factor, 25.8% patients had tubal factor and 1.6% had uterine factor infertility. In the present study 81% of patients had 2 embryos transferred, 14.5% had 3, 3.2% had single embryo transfer and only 1 patient had 4 embryos transfer. 40% of patients had IVF plus ICSI conception. 22.6% patients had frozen embryo transfer and 77.4% patients had fresh embryo transfer.

63% amongst IVF/ICSI group were singleton pregnancies and 33.8% were multiple pregnancies (p value-0.001) where as in controls 93.5% were singleton pregnancies and 1.6% had multiple pregnancies. In IVF/ICSI group, 95% of multiple pregnancies while 78% of singletons had obstetric complications. The miscarriage rate is 18% among IVF/ICSI group compared to 1.6% in control group (p value (0.02). 18% among cases and 1.6% among control group had first trimester bleeding p value (0.01). Among IVF group 9.6% patients developed OHSS. 3 patients had mild, 2 had moderate and 1 had severe OHSS. Among IVF/ICSI group 22.5% had cervical insufficiency compared to none among the control group (pvalue-0.002). However, the rate of congenital malformation and gestational hypertension was similar in the two groups. GDM was present in 14.5% among cases compared to 8.1% among controls. The incidence of placenta previa was 6.4% in cases compared to 1.6% in controls. There were 11.3% patients of PROM among cases compared to 1.6% among controls (p value-0.02). 33.8% patients had preterm delivery among cases compared to 14.5% in controls. 71% of patients among IVF/ICSI had caesarean section compared to 53% among controls Table 1.

Table 1 Comparison of mode of delivery.

Mode of delivery	Cases (%)	Controls (%)	P value
LSCS	44 (70.9)	33(53.2)	0.06
FTND	01 (01.6)	21 (33.8)	0.001
Abortion	11 (17.7)	01(1.6)	0.003
Ectopic	02 (03.2)	03(04.8)	1.00
PTVD	02 (03.2)	02 (03.2)	1.00
Hysterotomy	00	01 (01.6)	1.00
Induced MTP for anomalous baby	02 (03.2)	01(1.6)	0.47
Total	62 (100)	62 (100)	

Among IVF/ICSI out of 66 babies born 21.2% were VLBW, 44% were LBW, 10.6% were SGA, 42.4% were of normal weights compared to 5.3% of VLBW, 10.7% were LBW, 7.2% were SGA and 76.8% were of normal weights among controls. There is no difference between

the perinatal mortality between the two groups. The male: female ratio (1.53:1.07) was more among IVF/ICSI group compared to controls. There were 2 neonatal deaths in each group. The overall complication was higher among IVF/ICSI group compared to controls. Higher maternal age, nulliparity is seen in IVF/ICSI group. There is higher incidence of miscarriage, first trimester bleeding, cervical insufficiency, PROM and preterm deliveries and VLBW and LBW in IVF/ICSI group as compared to controls. Male: female ratio is higher among IVF/ICSI group. Table 2.

Table 2 Comparison of neonatal complications.

Neonatal complications	Cases (%)	Controls (%)	P value
No. of complications	69	31	0.04
Preterm	21(30.4)	09 (29.1)	0.43
Jaundice	08 (11.6)	04 (13.3)	0.36
Low birth weight	17 (24.6)	10 (33.3)	0.12
Very low birth weight	8 (11.6)	03 (10)	0.20
Respiratory distress syndrome	06 (08.7)	02 (6.6)	0.27
GERD	02 (02.8)	00	0.47
Sepsis	01(01.4)	00	1.00
Anemia	01 (01.4)	00	1.00
TTN	02 (02.8)	02 (6.6)	1.00
ROP	03 (04.3)	00	0.24
SGA	00	01 (3.3)	1.00

DISCUSSION

The incidence of infertility is around 10-15%. These couples require some form of assistance in conception, which may be in the form as minimal as ovulation induction or as intensive as IVF/ICSI. The number of pregnancies as a result of IVF/ICSI procedures exceeds 3 million in the world. Although most pregnancies after IVF result in normal healthy outcomes, an increased risk for a number of obstetric and neonatal complications, compared to naturally conceived pregnancies, has been variably reported.⁵

Increasing maternal age is a risk factor for obstetric and perinatal complications. The average age at which women attempt to conceive continues to rise, due to more women putting profession ahead of conceiving. Also, women who have had difficulty in conceiving are also older by the time they come for treatment with IVF. Older women are already predisposed to age related complications like GDM, hypertension etc.

Irregular cycles are more commonly seen in PCOS women due to oligo-ovulation and anovulation as a result of which the need for ART arises. PCOS is the most common endocrine syndrome affecting women of reproductive age with a prevalence of between 4-18% generally and up to 50% in South Asian women.⁶ PCOS

is more prevalent in obese women than those who are lean, affecting around 28% versus 5% respectively ($p=0.04$). It substantially contributes to infertility; in fact, it accounts for 90-95% of women attending infertility clinics with anovulatory cycles (Balen, RCOG. PCOS women are at increased risk of miscarriage, GDM, PIH, preterm-birth and perinatal mortality.^{7,8}

Initially, infertility was considered primarily a female problem and male infertility is often overlooked. The male infertility is on rising trend as seen in the study done by Hull MG et al, the percentage of male infertility was 32%, but in the study done by Manish B et al shows an incidence of about 40%.^{9,10} Also present study showed 40% of male infertility, as a result male infertility cannot be neglected. In the present study the ovarian cause of infertility is also higher, which may be due to decreased ovarian reserve in older women and increased incidence of PCOS due to unhealthy lifestyle. The incidence of tubal factor infertility is also increasing due to the increased prevalence of tuberculosis, PID and endometriosis. Increased incidence of PID is attributable to promiscuity. Genital tuberculosis accounts for 1-19% of infertility cases in India.¹¹ Incidence is still higher in women seeking assisted reproduction being 24.5% overall but as high as 48.5% with tubal factor infertility is reported by Singh et al.¹²

With the development of ART, the advent of ovarian stimulation to produce multiple oocytes and the transfer of multiple embryos in order to improve pregnancy and live birth rates, there has been an increase in the rate of multiple pregnancies. The incidence of multiple pregnancies is comparable to the study done by Gunby J et al and others.¹³ Following IVF/ICSI conception the miscarriage rate is higher than the spontaneous conception, this may be attributable to increased maternal age (Farr SL et al¹⁴), PCOS, hypothyroidism, overweight or obesity (Maheshwari A et al) etc. Both women's age and increased BMI have detrimental effect, but the same is observed in fertile population.^{14,15} The influence of the cause of infertility on miscarriages is also unclear.

Compared to spontaneously conceived pregnancies, IVF group had more miscarriage rate as similar to the study done by Philippe T et al (17.2%). IVF/ICSI conceived pregnancies are at high risk for first trimester bleeding.¹⁶ The reason of the above is unknown, however the influence of ovarian stimulation, luteal insufficiency and spontaneous embryo reduction are suggested. The technique of fertilization (IVF or ICSI) does not seem to be relevant (Ochsenkuhn R et al).¹⁷ The study by Petra De et al also showed higher incidence of about 17.6%, other studies showed much higher incidence than the present study (36.2% in Hofmann et al, 31.2% in Pezeshki et al.¹⁸⁻²⁰ It has been shown that first-trimester bleeding is correlated with an increased risk for miscarriage both in spontaneous (50% in Everett et al) and in IVF pregnancies. But in the present study only one

patient had miscarriage after first trimester bleeding among the IVF/ICSI group.²¹

Ectopic pregnancy rates have raised over the past decade although the reasons are unclear, improved and early diagnosis certainly has an effect. It is suggested that the history of PID (pelvic inflammatory disease), tubal factor of infertility and embryo transfer technique can lead to increased incidence of ectopic pregnancy. OHSS (Ovarian hyperstimulation syndrome) is iatrogenic complication, unique to IVF, following ovarian stimulation. The incidence of mild forms of OHSS are common, affecting up to 20-33% of in vitro fertilisation (IVF) cycles, 3-6% of IVF cycles are complicated by moderate and 0.1-2% by severe OHSS.²² OHSS is more commonly found in women with PCOS and with fresh embryo transfer group due to hormonal stimulation. Half of women who developed OHSS had PCOS among IVF/ICSI group.

Among IVF/ICSI group 22.5% had cervical insufficiency compared to none among the control group (p value-0.002) which is similar to the study done by Kazem et al (22.5%).²³ Increased operative interventions in the IVF/ICSI group may have led to the increased incidence of cervical insufficiency. Current information shows that IVF/ICSI pregnancies are associated with 1.5-fold increased risk of congenital abnormality (Ates and Buckett).²⁴ However it is unclear, whether this small increased risk is related to infertility itself or its treatment. In the present study, the rate of congenital malformation was similar in the two groups. The study done by Hansen et al and others also showed no significant statistical difference between case and controls.²⁵

There is reportedly an increased risk obstetric complication like GDM, pre-eclampsia, abruption, placenta praevia in IVF/ICSI group. The increased complications may be attributable to multiple pregnancies, older age group etc. The placenta praevia aetiology remains unclear, but several studies have reported higher frequencies of placenta praevia in pregnancies of women with advanced maternal age, multiparity and previous caesarean delivery or abortion. In a meta-analysis of complications related to assisted reproduction, the investigators reported three-fold higher risk of placenta praevia associated with the treatment (Jackson et al).²⁶ Increased caesarean section rates may be attributed to the increased associated complications, precious nature of pregnancy and anxiety on the part of the couples among cases.

Neonatal morbidity is higher among IVF/ICSI twin compared to singleton. However, IVF/ICSI singleton also shows higher incidence of preterm birth. The main reason for the morbidity is prematurity which leads to low birth weight babies, and increased rates of NICU admission. The increased incidence of preterm in IVF/ICSI pregnancies may be caused by the IVF technique per se,

the ovarian stimulation, or the infertility. The prevalence of preterm birth in the IVF group is almost 3 times higher than the control group. The difference between the two groups is statistically significant. The study done by Hung Chieh C et al also showed higher incidence of preterm birth in IVF pregnancies. It is commonest cause of perinatal morbidity.²⁷ The incidence among control group also showed higher incidence of preterm birth this is due to increased maternal complications like PIH, GDM which had led to preterm delivery at our hospital.

Multiple pregnancies contribute to almost one-third of all pregnancies conceived by IVF/ICSI. It constitutes almost 80% of preterm births among IVF group. Compared to singletons pregnancies multiple pregnancies have more number of low birth weight babies and thus more number of NICU admissions. The higher incidence of male babies after IVF may be attributable to the fact that male embryos divide faster than female embryos and selection of embryo is based on degree of cleavage.

CONCLUSION

Increased maternal age, nulliparity and obesity are more commonly seen in women undergoing IVF/ICSI pregnancies, all of which predispose to complications. Miscarriage rate is higher among IVF/ICSI conception. PCOS women are at increased risk of developing OHSS. IVF conceptions are associated with a significantly higher (one-third) incidence of multiple pregnancies. Prematurity is 3 times more in IVF/ICSI group, hence low birth weight babies and NICU admission rates is more common among IVF group. There is no difference in the incidence of congenital malformation between both groups. Perinatal mortality is not increased with IVF/ICSI conception. The male: female ratio is higher in IVF/ICSI conception.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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