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Original Research Article

A retrospective study of the comparison of maternal outcomes in *in-vitro*-fertilization pregnancy versus spontaneous conception

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ABSTRACT

Background: The adverse maternal outcomes of newer technology of IVF have not been studied so far, especially in India. The aim of the study was to compare maternal near miss and mortality between IVF-conceived and spontaneously conceived pregnancies, at a tertiary-level hospital, in Delhi.
Methods: We conducted a retrospective cohort study from 2018-2020. The demographic, obstetrics, past history, obstetric-related morbidity, mode of delivery, details of maternal near miss and mortality, and their reasons were recorded. Similar data from spontaneous conceptions were compiled. Comparison of maternal characteristics was tested using chi-square test, $p<0.05$ was considered significant.
Results: Mean age of women in the study group was 33.16±5.58 years and in controls was 26.16±4.28 years. The risk of multiple pregnancy (58.5% versus 2%, $p<0.0001$), pre-eclampsia (62.8% versus 17.1%, $p<0.0001$), gestational diabetes mellitus (23.5% versus 14.2%, $p=0.0493$), intrahepatic cholestasis of pregnancy (32.8% versus 10%, $p<0.0001$), antepartum haemorrhage (12.1% versus 2.85%, $p=0.0066$), preterm deliveries (66.4% versus 5.7%, <0.0001), and maternal near miss (12.8% versus 0.7%, OR 20.50, 95% CI-2.6979 to 155.8916, $p=0.0035$) were much higher in the study group as compared to the control group and was statistically significant. The odds of maternal mortality were 4.0882, 95% CI 0.4512 to 37.0465, $p=0.2105$ in the study group as compared to the control group.
Conclusions: There is a need to counsel couples wanting to conceive with IVF about not just the procedure and success rates of it, but also the potential for pregnancy complications.

Keywords: *In-vitro* fertilization, Maternal near miss, Maternal mortality, Spontaneous pregnancy

INTRODUCTION

Infertility has become one of the most serious global disabilities ranking fifth on the list.[1] The prevalence has been on the rise over the years and in India, it is around 3.9-16.8%. IVF has evidently helped innumerable couples so far which is reflected by an increase in the number of IVF centres across the country. Reproductive medicine specialists have always focussed primarily on perinatal outcomes following ART.

The second research topic so far in line has been the maternal risks of drugs used in various infertility protocols. The newer technology has brought along with it, adverse maternal outcomes, that have not been studied so far, especially in India. In a study done by Martin et al the odds of severe maternal morbidity were 1.8 times higher among singleton ART pregnancies compared with non-ART pregnancies during the intrapartum and postpartum period.[2] This study was planned with the aim to compare maternal near miss and maternal mortality in pregnancies conceived with IVF as compared to those conceived spontaneously delivering at our hospital.

METHODS

The present study was a retrospective cohort study planned over a period of three years (2018-2020) in the department

of obstetrics and gynaecology in a tertiary care referral hospital, New Delhi following clearance from ethical committee of our hospital. Our study enrolled a total of 280 women after fulfilling the inclusion and exclusion criteria. Among these, 140 women were cases i.e., IVF conceived pregnancies (use of autologous or donor oocyte/ sperm and embryo transfer) and 140 were controls i.e., women with spontaneous conception who delivered in the study period. Sample size was calculated using the Epi-info tool for cohort study using 1-α as 95%, power of the study as 80%, percent of exposed with outcome (maternal near miss) as 5.7%, and odds ratio for maternal near miss as 3.61 from one of the previous studies, Cromi et al.[3] Sample size was calculated as 115 for both IVF conceived pregnancies and spontaneous conception, so total sample size was 230. The details of IVF conceived women who delivered in our hospital were taken from medical record section. The proforma was filled with details including maternal age, duration of marriage, parity, gestational age, relevant past history of tuberculosis or abdominal/pelvic surgery, number of foetus (single, twins, triplets). Obstetrical outcomes i.e., anaemia (haemoglobin <11 gm%), pregnancy induced hypertension (blood pressure more than 140/90 mmHg on two occasions 4 hours apart or single recording of more than 160/110 mmHg with or without signs of severe pre-eclampsia), chronic hypertension, gestational diabetes mellitus (deranged oral glucose tolerance test/ glucose challenge test), intrahepatic cholestasis of pregnancy(history of pruritis over palms and soles, serum bile acids >10 micromol/L), hypothyroidism, preterm delivery/preterm premature rupture of membranes (delivery/leaking before 37 completed weeks of gestation) or term delivery (>37 weeks), antepartum haemorrhage and its causes were also noted.

Mode of delivery, indications in cases of caesarean section, baby status (live or dead), complications in the intrapartum period, need for blood transfusion, and postpartum complications if any (postpartum haemorrhage, defined as any blood loss greater than 1000 ml within the first 24 hours after childbirth, ICU admission not including admission only for observation, hysterectomy, sepsis, cardiorespiratory failure) were also recorded. Maternal near miss or maternal mortality were labelled as per the WHO definition and their causes were noted.[4]

Maternal near miss is defined as when a woman who nearly died but survived a complication that occurred during pregnancy, childbirth, or within 42 days, and maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy from any cause related to or aggravated by the pregnancy or its management. The total duration of stay in the hospital was also noted. Similar data from spontaneous conceptions was compiled which were an admission just after the IVF conceived pregnancy from the admission entry register of the obstetric ward to avoid any selection bias. All the data was compiled in a Microsoft excel sheet by the investigator and statistically analysed.

The quantitative variables were expressed as mean ± SD and qualitative variables as percentages. Comparison of maternal characteristics in terms of obstetrics history and intra and postpartum events was tested using chi-square test, p value less than 0.05 was considered as significant.

RESULTS

Maternal characteristics, medical, and obstetric history, and outcomes in both study and control groups are detailed in Table 1. The average age in the study group i.e., IVF conceived pregnancy was 33.16±5.58 years, and in controls was 26.16±4.28 years. The average duration of married life at the time of conception was 11.2 and 4.7 years in the study and control group respectively. The majority i.e., 85% (119/140) were primigravida in IVF conceived pregnancy whereas average parity in controls was 1.75. The study group had a positive history of tuberculosis in 16 (11.4%) and history of abdominal/pelvic surgery in 14 (10%). Women in IVF conceived group were more likely to have multiple pregnancy (58.5% as compared to 2% in controls, odds ratio 45.23, 95% CI 13.8492 to 147.7170, p<0.0001), chronic hypertension (18.5% as compared to 1.42% in controls, OR-1.451, p=0.2384) and preterm delivery either spontaneous or induced (66.4% versus 5.7% in control group, OR 32.64, 95% CI=14.7407 to 72.3138, p<0.0001). The majority (80%) IVF conceived pregnancies underwent caesarean section. Out of these, 45/112(40%) had caesarean section due to first breech in twins or due to triplet pregnancy, 25% due to doppler abnormalities (AEDF/REDF), 7% each due to placenta previa, severe pre-eclampsia with poor bishops and failed induction.

Two had caesarean section in view of previous history of myomectomy with endometrium breech and 1 had an emergency caesarean due to cardiopulmonary arrest to aid in maternal resuscitation (unfortunately, the patient had not survived due to massive pulmonary embolism). Postpartum haemorrhage was seen in 27.6% of IVF conceived pregnancies and 2.8% in controls (OR=9.6697, 95% CI=3.3123 to 28.2293, p<0.0001) and was found to be highly significant.

Similarly, the need for blood transfusion was 4 times more in the study group as compared to controls (OR=3.9739, 95% CI=1.9749 to 7.9961, p=0.0001). In the entire cohort, total of nineteen cases (13.5%) of maternal near miss were identified, and five maternal deaths. Individual causes are highlighted in Table 2.

The rates of maternal near miss among the study group was significantly higher than the control group (12.8% versus 0.7%, OR=20.50, 95% CI=2.6979 to 155.8916) and p=0.0035. The odds of maternal mortality were 4.0882, 95% CI=0.4512 to 37.0465, p=0.2105 in the study group as compared to the control group.

Table 1: Maternal characteristics, medical, obstetric history and outcome.

Characteristics	Study group (n=140), (%)	Control group (n=140), (%)	Odds ratio	P value
Age at conception (In years)				
< 35	98 (70)	137 (97)		
36-40	30 (21)	2 (1.4)		
41-45	9 (6.4)	1 (0.7)		
>46 years	3 (2.1)	0		
Pre-existing medical diseases/ significant past history				
Chronic hypertension	26 (18.5)	2 (1.4)	1.4514	0.2384
Overt diabetes mellitus	15 (10.7)	8 (5.7)	1.9800	0.1335
History of TB	16 (11.4)	2 (1.4)	9.0323	0.0038
Obstetrical complications				
Multiple pregnancy	82 (58.5)	3 (2.14)	45.2302	<0.0001
Pregnancy induced hypertension	88 (62.8)	24 (17.1)	8.1795	<0.0001
Gestational diabetes	33 (23.5)	20 (14.2)	1.8505	0.0493
IHCP	46 (32.8)	14 (10)	4.4043	<0.0001
Anaemia	28 (20)	24 (17.1)	1.2083	0.5391
APH	17 (12.1)	4 (2.85)	4.6992	0.0066
Preterm premature rupture of membranes	26 (18.5)	6 (4.28)	5.0936	0.0005
Preterm delivery (spontaneous/iatrogenic)	93 (66.4)	8 (5.7)	32.6489	<0.0001
Outcome				
Gestational age at delivery (in weeks)	33.5	37.6		
Induction of labour	32 (22.8)	37 (26.4)	0.8248	0.4884
Caesarean section	112 (80)	57 (40)	5.8246	0.0001
Intrauterine demise or abortion	11	5	2.3023	0.1317
Postpartum haemorrhage	31	4	9.6697	<0.0001
Blood transfusion (Antepartum+ postpartum)	38	12	3.9739	0.0001
Duration of hospital stay (in days)	14.6	7.3		

Table 2: Maternal near miss and maternal mortality with their causes.

Characteristics	Study group, (n=140) (%)	Control group, (n=140) (%)	Odds ratio	P value
Maternal near miss	18 (12.8)	1 (0.7)	20.5082	0.0035
Causes* (multiple factors in one case)				
Postpartum hysterectomy	3	0		
Blood transfusion (>5 units of red cells)	8	0		
Intubation/ventilation >60 minutes unrelated to anaesthesia	12	1		
Use of vasoactive drugs	14	0		
Hypertensive emergency	3	0		
Maternal mortality	4 (2.85)	1 (0.7)	4.0882	0.2105
Causes				
Amniotic fluid embolism	1	0		
Pulmonary embolism	3	0		
Acute pancreatitis	0	1		

DISCUSSION

Multiple factors have over the years attributed to increased use of artificial reproductive technologies (ART) for conception. The newer technology has its advantages as well as disadvantages. The same applies to ART as well. ART has been a ray of hope for innumerable infertile couples but on the other hand, it has brought many complications which can cause havoc in the life of mother.

National ART surveillance system from US and Europe analysed the safety outcomes of IVF to a narrow set of complications resulting from multiple births, low birth weight infants, and preterm delivery without giving any significant consideration to maternal health (Dyer et al 2016, ESHRE 2018).[5] Our study aimed to study the comparison of maternal outcomes in *in-vitro*-fertilization pregnancy versus spontaneous conception.

The mean age of women in our study group was 33.16±5.58 years with the youngest mother being 19 years of age. The average age in our study group is lesser as compared to previous studies by Tane et al (36.2 years), Bergh et al (36.5 years), and Modi et al (38.5 years).[6-8] This finding could be amenable to increased awareness among the population nowadays regarding the availability of ART services. The centers of ART have flourished and even financial support is now extended to needy couples in the form of loans to avail the services.

As the demand increases malpractices routes in. The same has been done in ART industry as well. At present it is a 30 billion rupees industry with over 3000 centres across India. Over all these years, ICMR 2010 along with the ministry of health and family welfare have made attempts to pen down guidelines to curtail any sort of malpractices. Malpractices that still prevailed were the transferring of a greater number of embryos than required and incomplete evaluation of the mother's health prior to proceeding with IVF and no check on the maximum desirable age of the mother by many ART centres. Various cases of women conceiving with IVF in their 60's and 70's have been reported Emmerson PB 2008. The fate of such a child is not known as they might not be taken care of properly as it mandates. The new ART law that came in India in December 2021 aims to keep a check on the mushrooming ART centers in the country along with various critical aspects of the procedure and the persons involved.

The unchecked number of embryo transfers in the greed of increasing the success rate of IVF cycle and the request of the desiring parents who desire pregnancy at any cost leads to a high risk of multi-foetal pregnancy. In our study, 58.5% of cases of IVF conceived pregnancy had multifetal gestation as opposed to 2.14% in the control group. In a study by Modi et al and Bergh et al the risk of multifetal gestation in the study and control group was 40.7% vs 5.5% and 26.95 vs 1% respectively. In a retrospective multicentre cohort study by Tan et al 18.7% of women conceived via IVF had multiple pregnancies versus only 1.53% of spontaneous conception ($p<0.001$).[7-9]

Increased risk of gestational diabetes mellitus has been observed in many studies done so far similar to that observed in our study. The most probable reason sighted is the high prevalence of polycystic ovarian syndrome in females with infertility.[10]

IVF pregnancies owing to the baseline differences in the process of placental development during the formation of chorion *in vitro* lead to all varieties of abnormalities associated with abnormal placental vasculature. These include pregnancy induced hypertension, foetal growth restriction, placenta previa, accreta, percreta, and abruption. In our study, PIH was found in 62.8% IVF conceived women as compared to 17.1% in the control group. In a study by Modi et al an increased risk of PIH was found in IVF conceived pregnancies; 22% versus 5% in spontaneous conception, and in a study by Maman et al the risk of PIH was 14%, and 4% in study and control group respectively.[8,10] The odds of developing intrahepatic cholestasis of pregnancy in the control group was 4.4 which was found to be highly significant; $p<0.0001$ in study done by Jackson and Modi et al.[8,11]

The risk of preterm delivery was found to be 22% in IVF conceived pregnancy group in a study by Modi et al 25% in a study by Tan et al as compared to our study where it was much higher; 66.4%.[8,9] The most probable reason behind this is higher percentage of multiple pregnancies and pre-eclampsia in our study which could be the reasons for both spontaneous as well as iatrogenic premature deliveries. Owing to this reason, along with placental abnormalities in the form of abnormal placentation as well as uteroplacental insufficiency the rate of caesarean delivery in the study group was 80% which was double as compared to the control group in our study, and the difference was found to be highly significant, $p=0.0001$. In previous studies by Modi et al and Tan et al the caesarean delivery rate in IVF conceived pregnancy versus spontaneous conception was 75% and 3%; 51% and 12% respectively.[6]

Postpartum complications during the hospital stay in both groups are highlighted in Table 3.

Table 3: Postpartum complications during the hospital stay.

Variables	Study group, (n=140) (%)	Control group, (n=140) (%)
Secondary postpartum haemorrhage	2 (1.42)	0
Post-operative fever	6 (4.28)	4 (2.85)
Surgical site infection	5 (3.57)	4 (2.85)
Rectus sheath hematoma (conservative management)	1 (0.7)	0
Gluteal abscess	2 (1.42)	0
Facial palsy	1 (0.75)	0
Garde IV retinopathy (Hypertensive/ diabetic)	2 (1.425)	1 (0.7)
PRES (Posterior reversible encephalopathy syndrome)	1 (0.7)	0
Obstructive jaundice	0	1 (0.7)

Maternal mortality is one of the most important indicators for measuring maternal health and the development of the nation. Maternal near miss determines a link between optimum management and the loss of a mother's life as per WHO.[12] It is defined by various criteria, one of the most important among them is management criteria. It includes: Use of continuous vasoactive drugs. Postpartum or post-abortion hysterectomy due to haemorrhage or infection. More than 5 units of transfusion of red cells. Intubation or ventilation for a period of more than 60 minutes unrelated to anaesthesia. Need for dialysis for treatment of acute renal failure and need for cardiopulmonary resuscitation.

As per the sample registration system report of India, the maternal mortality ratio has reduced to 113/100,000 live births as compared to 130/100,000 live births in 2014-16.[13] A survey on maternal mortality by FOGSI 2003 revealed the leading causes of maternal deaths. These were hypertension (29.4%), haemorrhage (21.5%), sepsis (15%), and medical disorders (12%). The contribution of ART to these causes is largely unknown, but increasing the use of ART among high-risk women will increase these risks exponentially.

In our study, maternal near miss and mortality was found to be much higher than in previous national and international studies.[3,8] The most common reason behind this is that our hospital is a tertiary referral hospital for all kinds of high-risk cases from nearby states. Our study group also had an increased risk of pre-eclampsia as well as antepartum haemorrhage including both placenta previa (58.8%) and abruption (41.7%). These are the two indications that can lead to severe morbidity and even mortality. All four deaths in the study group shared certain characteristics elaborated in Table 4. In a study by Modi et al, 6 IVF conceived women needed admission to a high dependency unit, and two mortalities were reported both due to amniotic fluid embolism. No mortality was reported in the control group in this study.[8] A study by Cromi et al found that the crude prevalence of potentially life-threatening conditions and maternal near miss were higher among IVF conceived pregnancies than spontaneous conception (27.1% versus 5.7%) and (2.6% versus 0.3%).[3] In a study by Tan et al univariate analysis showed a statistically significant association between IVF and higher risks of severe maternal morbidities (SMM) (OR-1.69, 95% CI 1.14-2.49).[9] They analysed that multiple pregnancy was the main contributory factor that resulted in an increase in the risk of SMM and this does not occur in the case of singleton pregnancy, but a relatively wide CI (confidence interval) cannot refute the possibility of increased risk of SMM completely in singleton IVF conceived gestation. No mortality was reported in this study as well. Similar large database studies done prior to the study by Tan et al concluded an increased risk of SMM among IVF conceived pregnancies, more likely in the presence of multiple gestation. These studies were by Wang et al, which enrolled 6543 IVF conceived women and another study by Martin et al was from USA which enrolled 1, 0, 16 and 618 women from a database from 2008-2012.[2,19]

Table 4: Maternal characteristics in case of maternal deaths.

Age (In years)	Donor oocyte	Multiple pregnancy	Chronic HTN	Severe PE	Overt DM	Caesarean section	Atonic PPH	BT	Time of death
50	Yes	No	Yes	Yes	Yes	Yes (FGR with breech)	No	No	Within 12 hours post-caesarean
36	Yes	Yes	Yes	Yes	No	Yes (cardio-pulmonary arrest due to? Pulmonary embolism- for resuscitation)	No	No	Within 8 hours post-caesarean
35	Yes	Yes	Yes	Yes	Yes	Yes (Foetal distress)	Yes	Yes	Within 12 hours post-caesarean
48	Yes	No	Yes	No	Yes	Yes (Breech)	No	Yes (pre-op anaemia)	Within 12 hours post-caesarean

Artificial reproductive technology act, 2021, aims to establish a national registry of all ART clinics and banks which acts as a central database containing details of all clinics, services provided, and outcomes of services. The authors would like to highlight the fact that maternal follow-up after IVF procedure should be for at least 42 days post-delivery and the same should be entered in the central database. This exercise will enable us to analyse the effect of ART on maternal health on a wider scale which is one of the limitations of our study. This will assist in modifying existing guidelines more meticulously to be fruitful for needy couples. Further, it will be interesting to compare the maternal outcomes before and after the introduction of new ART laws, in 2021 in India in near future.[15]

CONCLUSION

With the rising number of infertility rates, more number of couples are seeking IVF pregnancy. Undoubtedly it has given hopes and smiles to numerous couples and their families, but it comes with a cost, the cost of increased pregnancy complications, morbidity, and in some instances, mortality. There is a need to counsel couples wanting to conceive with IVF about not just the procedure and success rates of it, but also the potential for pregnancy

complications. Also, newer methods, with fewer complications should be researched for.

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