

Maternal and Perinatal Outcome in Pregnancies Following Infertility

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ABSTRACT

Context: General practitioners as well as obstetricians are coming across a large number of pregnant women whose conceptions are following a period of infertility or treatment for the same. There is a controversy in the literature regarding the occurrence of adverse outcomes of pregnancy in such women.

Aims: To assess the maternal and perinatal outcome in pregnancies that occurred after a period of infertility and to compare the outcome in spontaneous conceptions with the conceptions following treatment for infertility.

Settings and Design: Retrospective analysis of hospital records of 200 pregnancies following infertility during the year 2009 in a tertiary care center in South India.

Material and Methods: All the women were divided into two groups, viz: Group 1—those who had history of infertility but conceived spontaneously and Group 2—those with history of infertility and conceived only after treatment for infertility. The main outcome measures were antenatal complications and adverse neonatal complications.

Statistical analysis: The statistical package SSPS version 15.0. Chi-square and student 't' test was used for nonparametric and parametric variables.

Results: The incidence of hypertension was 60% and that of gestational diabetes was 7%. Obstetric complications included increased incidence of preterm labor (23.5%) and premature rupture of membranes (38%). There was no statistically significant difference in both groups though the medical complications especially hypertension was high in the pregnancies following spontaneous conceptions, i.e. untreated group. There was a greater demand for the NICU care mainly because of prematurity. The PNMR was (40/1000) less than the institutional rate of 72/1000 births.

Conclusions: There is increased incidence of hypertension premature rupture of membranes and preterm delivery in pregnancies following infertility. There is no significant statistical difference in the adverse pregnancy outcomes between spontaneous conception and those treated for infertility.

Key Messages: Pregnancies following infertility are at increased risk of developing hypertension and preterm labor and hence these women should be screened for the same and preventive measures to be undertaken to achieve good maternal and perinatal outcome.

Keywords: Infertility, Spontaneous conception, ART Medical and obstetrical complications, Neonatal outcome.

INTRODUCTION

In recent years, as the problem of infertility is increasing, every obstetrician comes across pregnancies after the treatment for infertility with increasing frequency. Adverse obstetrical and perinatal outcomes are being reported in such patients.^{1,2} The increase in risks may be due to the pathophysiology underlying infertility itself, treatment employed for achieving pregnancy and sometimes may be due to advanced maternal age. However, few studies have stated that singleton gestations following infertility appear to have no higher risk for complications than do those of

normal fertile controls.³ Hence, this retrospective study was undertaken with the following objectives:

1. To assess the maternal and perinatal outcome of pregnancies following infertility.
2. To compare pregnancy outcome between spontaneous conceptions following infertility and conceptions following treatment for infertility.

SUBJECTS AND METHODS

The maternal records of patients, who had intranatal care in JIPMER Hospital (a tertiary care center in South India mainly catering to rural population) during the year 2009 were analyzed with respect to the above objectives.

There were 200 patients, who delivered during this period from January 2009 to December 2009. They were divided into 2 groups, viz: Group 1—those, who had history of a period of

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infertility but conceived spontaneously and Group 2—those with history of infertility and conceived only after treatment for infertility (ovulation induction alone, IUI or IVF). Data was collected regarding age of the women, duration of infertility, type of infertility (primary or secondary), parity, medical diseases that developed during pregnancy, obstetrical problems and gestational age at delivery, mode of delivery, fetal and neonatal outcome, etc. The main outcome measures were antenatal complications and adverse neonatal complications. The two groups were compared with respect to the above outcomes. Statistical analysis was done using the statistical package SSPS version 15.0. Chi-square and student 't' test was used for non-parametric and parametric variables. A p value of 0.05 was considered significant.

RESULTS

The mean age was 28.9 years and the mean duration of infertility was 8 years. There were 153 (76.5%) women with primary infertility and 47 (23.5%) with secondary infertility. Thirteen percent of women with secondary infertility suffered from a prior abortion and 2.5% had recurrent abortions. The clinical profile of patients in the two groups is shown in Table 1. There was no statistical difference in the two groups with respect to age, mean duration of infertility and mean gestational age at delivery. Table 2 shows the medical disorders complicating

pregnancies. The most common medical complication was hypertension during pregnancy. Gestational hypertension and pre-eclampsia were more common in spontaneous conception group (Group 1) than in group 2 but not significant statistically. The incidence of hypertension is very high (59.5%) when compared to general population of all pregnant women (12%). Anemia was also more common in group 1 when compared to group 2. The incidence of anemia was only 33% as most of them had regular antenatal care. The incidence of gestational diabetes was 7% marginally high than the general pregnant population. GDM was high in group 2 when compared to group 1 though statistically not significant. The obstetric complications encountered are represented in Table 3. Preterm delivery and postdated pregnancy were doubled than in general pregnant population and there is not much statistical difference in two groups except that postdated pregnancy was less common in group 2. Similarly, the occurrence of multiple pregnancy was more common in group 2 as expected. Premature rupture of membranes (PROM) was more common (48%) than in general pregnant population. IUGR was diagnosed only in 8.5% of the pregnancies reflecting the good antenatal care that a woman seeks following conception after period of infertility.

Table 4 shows the management of delivery in these women. 32 percent of women required induction of labor and those women belonging to group 1 required induction more often

Table 1: Clinical profile

| Characteristics | Group 1–116 (58%) | Group 2–84 (42%) | p value |
|------------------------------|----------------------|---------------------|---------|
| Mean age (years) | 28.7 ± 3.5 | 29.19 ± 3.6 | 0.510 |
| Mean gestation | 38.2 ± 2.3 | 37.81 ± 2.4 | 0.319 |
| Mean duration of infertility | 8.07 ± 3.5 | 7.96 ± 3.3 | 0.452 |
| Primary infertility | 92(46%) | 61(30.5%) | 0.801 |
| Secondary infertility | 24(12%) | 23(11.5%) | 0.567 |
| Regular cycles | 82(70.7%) | 60(71.5%) | 0.6 |
| Irregular cycles | 34(29.3%) | 24(28.5%) | – |

Table 2: Medical complications

| Parameter | Total no. of cases (200) | Group 1 (116) | Group 2 (84) | p value |
|-------------------------------|-----------------------------|---------------|--------------|---------|
| Gestational HTN | 85(42.5%) | 53(45%) | 32(38%) | 0.280 |
| Pre-eclampsia | 34(17%) | 21(18%) | 13(15%) | 0.651 |
| Hypothyroid | 6(3%) | 4(3.4%) | 2(2.3%) | 0.600 |
| Gestational diabetes mellitus | 14(7%) | 5(4.3%) | 9(10.4%) | 0.160 |
| Anemia | 66(33%) | 45(38%) | 21(25%) | 0.66 |

Table 3: Obstetric complications

| Complications | Total no. of cases (200) | Group 1 (116) | Group 2 (84) | p value |
|----------------------------------|-----------------------------|---------------|--------------|---------|
| Preterm labor | 43(23.5%) | 23(19%) | 20(23%) | 0.47 |
| Postdated pregnancy and delivery | 45(22.5%) | 30(25%) | 15(17%) | 0.18 |
| PROM* | 76(38%) | 41(35.3%) | 35(41.6%) | 0.36 |
| Antepartum hemorrhage | 3(1.5%) | 3(2.5%) | Nil | – |
| Multiple pregnancy | 12(6.5%) | 3(2.5%) | 9(10.7%) | 0.14 |
| IUGR** | 17(8.5%) | 10(8.6%) | 7(8.3%) | 0.66 |
| Malpresentation | 12(6%) | 7(6.0%) | 5(5.9%) | 0.56 |

*PROM-Premature rupture of membranes; IUGR** Intrauterine growth restriction

(46.5%) when compared to group 2 (26.6%) though statistically not significant. The rate of cesarean section is also high (31%) in these women compared to 16% of our institution rate during this period of study. There was no difference in the rate of cesarean section between two groups. The rate of instrumental delivery is also doubled in these women 18% when compared to 9% of institutional rate. Women in group 2 required assistance with instruments more often (21.4%) than in group 1 (15.5%). The neonatal outcome is shown in Table 5. There is no difference in mean birth weight, Apgar score and the incidence of congenital anomaly in both groups and when compared to general neonatal outcome. But 30.5% of the neonates were admitted to the NICU. More numbers of neonates were admitted to NICU in group 2 (36.9%) when compared to group 1 (25.8%). This was also not significant statistically. There were 2 neonatal deaths in group 2 compared to 5 in group 1.

The perinatal mortality rate was less (40/1000 live births) when compared to the hospital PNMR (64/1000 live births) during this period. The causes of perinatal deaths were congenital anomaly in 3, prematurity in 2 and meconium aspiration syndrome in 2. Congenital anomalies included 2 cases of conjoint twins and one case of encephalocele, which were in spontaneous conception group (Group 1). There were no congenital anomalies in group 2 and the two neonatal deaths were due to meconium aspiration syndrome. 10 percent of the neonates required NICU care for meconium aspiration syndrome out of which 2 succumbed.

DISCUSSION

Pregnancies in women with infertility have been reported to be associated with adverse maternal as well as perinatal outcomes since 1990s. A large review, which compared the obstetric and perinatal outcomes of pregnancies in unexplained infertility with that of pregnancies in general population reported a statistically significant increase in incidence of pre-eclampsia, abortion

and preterm labor. There was also increased incidence of induced labor and cesarean deliveries. The mean duration of pregnancy and apgar scores though lower in the pregnancies of unexplained infertility, though not statistically significant when compared to neonatal outcome of general population.¹ The mean age of the women with infertility in the present study is 29 years, which is very close to the mean age of 30.8 years in the review of Pandian and colleagues. A prospective follow-up study of 70 unexplained infertile couple, which compared the obstetric outcome in treated and untreated group reported a very high incidence (25%) of multiple pregnancies in treatment group when compared to 2.8% in spontaneous conception group.⁴ In the present study, the incidence of multiple pregnancies is only 10.7% in the treatment group when compared to 2.5% in the spontaneous conception group. But this is higher than that reported in the review (6% vs 0.36%) by Pandian and colleagues and almost similar to that reported by Yasmin and colleagues (11%).⁵

MEDICAL COMPLICATIONS

The commonest medical complication found in the present study is very high incidence of gestational hypertension (GHT) and pre-eclampsia (PE) in both the groups (spontaneous conception vs treated group—45% vs 38%; 18% vs 15% respectively). Yasmin and colleagues reported a overall incidence of PIH/ pre-eclampsia in both treated and untreated groups to be 32%. But in the review of Pandian and colleagues, the incidence of pre-eclampsia was very low (5%) though they encountered one case of eclampsia in the spontaneous conception group. The next common medical problem found in the present study was anemia (33%) and it was more common in spontaneous conception group (38%) when compared to 25% in treated group. This reflects the care, which a woman takes after conception following a period of infertility as the incidence of anemia in pregnancy of general population is as high as 80 to 90%.

Table 4: Mode of delivery

| Parameters | Frequency | Group 1(116) | Group 2 (84) | p value |
|----------------------------|-----------|--------------|--------------|---------|
| Spontaneous labor | 37(18.5%) | 19(16.3%) | 18(21.4%) | NS |
| Induced labor | 76(31.5%) | 54(46.5%) | 22(26.6%) | NS |
| Elective cesarean section | 6(3%) | 3(2.5%) | 3(3.5%) | NS |
| Emergency cesarean section | 56(28%) | 34(29.3%) | 22(26.1%) | NS |
| Instrumental delivery | 36(18%) | 18(15.5%) | 18(21.4%) | NS |

Table 5: Perinatal outcome

| Parameters | Total no. of cases (200) | Group 1 (116) | Group 2 (84) | p value |
|-------------------|--------------------------|---------------|--------------|---------|
| Mean birth weight | 2.65 ± 0.06 | 2.62 ± 0.06 | 2.69 ± 0.06 | NS |
| Mean Apgar 1' | 7.2 ± 1.56 | 7.05 ± 1.8 | 7.42 ± 1.1 | NS |
| Apgar 5' | 8.4 ± 1.60 | 8.22 ± 1.9 | 8.63 ± 1.09 | NS |
| NICU admission | 61(30.5%) | 30(25.8%) | 31(36.9%) | NS |
| Meconium liquor | 20(10%) | 11(9.4%) | 9(10.7%) | NS |
| Cong. anomaly | 3(1.5%) | 3(2.5%) | — | NS |
| Neonatal death | 7(3.5%) | 5(4.3%) | 2(2.3%) | NS |

PNMR—40/1000 live births

Gestational diabetes was found to be twice common in group 2 when compared to group 1. This may be explained, if the treated group constituted more of patients with PCOS. A prospective cohort study of pregnancy outcome in PCOS patients reported GDM in 12.8%.⁶ In the present study, the overall incidence of GDM is 7% (4.3% in spontaneous conception and 10.4% in treated group) but the total number of PCOS patients is not exactly known. This incidence of 7% GDM in the present study is consistent with that reported by Yasmin and colleagues. A study, which compared the outcome of pregnancy in women with PCOS and pregnancy in normal fertile women found an increased risk of gestational diabetes and pregnancy-induced hypertension in women with PCOS.⁷

OBSTETRIC COMPLICATIONS

In the present study, the incidence of preterm labor as well as postdated pregnancy is increased two fold when compared to general obstetric population. Postdated pregnancy was more common in spontaneous conception group than the treated group though it was not statistically significant. Yasmin and colleagues also reported the increased incidence of preterm labor (18% vs 7% background risk) to have risen to 2.6 fold. There were no reports on postdated pregnancies. In the present study, the incidence of postdated pregnancies is also high (22.5%) when compared to general population (10%). In the treated group 17% were postdated pregnancies against 25% in the spontaneous conception. This high incidence may be due to irregular cycles, which were almost equal in both the groups (Table 1). The incidence of premature rupture of membranes is also increased when compared to general obstetric population and its incidence is 41.6% in treated group when compared to 35.5% of spontaneous conception group in the present study. Yasmin and colleagues reported an increased incidence of around 2.3 fold in preterm premature rupture of membranes.

There were no cases of antepartum hemorrhage in treated group and there were only 3 cases out of 116 of spontaneous conception group constituting 1.5%, which is almost similar to that of general population. This is in contrast to the study of Yasmin and colleagues, who reported 6% incidence of antepartum hemorrhage against a background risk of 3%. IUGR was found to be less common in the present study amounting to only 8.5% in contrast to other studies. Yasmin and colleagues reported 24% of pregnancies to be having IUGR.

OUTCOME OF PREGNANCY AND LABOR

Only 18.5% had spontaneous onset of labor. The incidence of induced labor is high in spontaneous conception group as the incidence of postdated pregnancy was higher in this group. Overall 31.5% required induction of labor in the present study, which was consistent with the 28% incidence of induction reported by Pandian and colleagues. The rate of instrumental deliveries was similar in both groups and overall 18% underwent instrumental deliveries, which was slightly higher than the average of 12% incidence of our institution during the study period. Only 3% of patients were taken up for elective LSCS in

the present study, which was less than the report of 6% in the study of Pandian and colleagues. The overall rate of cesarean section was high (31%) when compared to the average cesarean section rate of our institute during the period, which was 17%. In the study of Pandian and colleagues, 26% required cesarean section of which 20% were emergency cesareans. In the present study, 28% underwent emergency cesarean and the most common indication was fetal distress. A prospective study aimed to find out the antepartum complications and neonatal outcome involving 411 women reported an increased rate of emergency cesarean section without any increase in antenatal complications.⁸

FETAL OUTCOME

The mean birth weight in the present study was 2600 gm and this finding correlates with the incidence of IUGR, which was low. The mean birth weight was 2900 gm in the study of Yasmin and colleagues and it was 3300 gm in the study of Hassan Zahraei and colleagues.⁶ There was no difference of birth weight in the spontaneous conception group and treated group in the present study, whereas Isaksson and Aila reported a statistically significant difference in both the groups with higher birth weight in spontaneous conception group.⁴ In the present study, the rate of NICU admission (30.5%) is increased because of higher incidence of preterm birth and as well as postdatism giving rise to meconium stained liquor and subsequent aspiration. Only 10% of the neonates required NICU admission in the study of Pandian and colleagues. In the study of Hassan Zahraei and colleagues, 21.3% of neonates required NICU admission when compared to 11% controls. The PNMR was (40/1000) less than the institutional rate of 72/1000 births. The seven perinatal deaths out of 200 were due to meconium aspiration syndrome in 3, prematurity in 2 and congenital malformations in another 2. The still birth rate was 1.36% and congenital anomalies were 0.4% in study of Pandian and colleagues. In the present study, there were no still births and all the seven were neonatal deaths.

The evidence based guideline regarding pregnancy outcome in infertile women published by the Society of Obstetricians and Gynecologists of Canada and the Board of the Canadian Fertility and Andrology Society is at level 2A.⁹ Spontaneous pregnancies in untreated infertile women may be at higher risk for obstetrical complications and perinatal mortality than spontaneous pregnancies in fertile women. The findings of the present study are consistent with this though the perinatal mortality is less than the spontaneous pregnancies in general population. This may be due to the elimination of congenital malformation by good antenatal care and also due to early diagnosis of fetal compromise during intranatal period.

The pregnancies achieved by assisted reproduction are at higher risk than spontaneous pregnancies for adverse perinatal outcomes, including perinatal mortality, preterm delivery, and low birth weight, and close surveillance during pregnancy should be available as needed (II-2A). The present study has not looked into this aspect because only few pregnancies after ART were cared for in this institute. The frequency of premature deliveries,

IUGR and perinatal mortality was reported to be increased in pregnancies, which resulted after treatment for infertility in a study involving 691 subjects.¹⁰ In the present study preterm deliveries were high but not IUGR and perinatal mortality can still be reduced with proper management of deliveries with meconium stained liquor.

CONCLUSION

The present study revealed a very high incidence of medical complications, such as gestational hypertension, pre-eclampsia and gestational diabetes in pregnancies following infertility. There is also increased incidence of obstetric complications especially preterm labor and premature rupture of membranes. The incidence of operative vaginal delivery as well as emergency cesarean section is also increased significantly. There is increased need for neonatal intensive care requirement.

There is no significant statistical difference in the rate of complications in the spontaneous conception group and those conceived after the treatment for infertility though the incidence of hypertension during pregnancy is high in spontaneous conception group and gestational diabetes mellitus and multiple pregnancies is high in the treated group. The incidence of induced labor is high in spontaneous conception group because of increased pregnancies with postdatism.

Limitations of the study:

1. Retrospective analysis.
2. The incidence of PCOS is not exactly recorded in all cases, hence it could not be correlated with the medical complications that were diagnosed.
3. The pregnancies following ART were very few to reach any conclusions.

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