

Type of Conception and Outcomes in Women with Singleton Pregnancy

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ABSTRACT

Background: An estimated 4.9 million women in India are infertile. If we add secondary infertility to these estimates, the number of infertile couples in India may rise to 17.9 million. Increased use of assisted conception services and information on outcomes after assisted conceptions are useful, to appropriately counsel women who utilize such services.

Aim: To determine as to whether outcomes of pregnancy differ between assisted conceptions and natural conceptions in pregnant women with singleton foetuses.

Settings and Design: A retrospective observational study done a single tertiary care centre in southern India.

Materials and Methods: This study included pregnant women with singleton gestations, who delivered at the study institute in 2012. Assisted conception was considered to include all invasive and non-invasive methods like ovulation induction (OI), Intrauterine insemination (IU), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI). Outcomes of interest included gestational age at delivery, birth weight, small for gestational age babies, still births, neonatal deaths and caesarean sections. Point estimates and the 95% Confidence Intervals (CI) around point estimates

of associations with assisted conceptions and outcomes were determined by using bivariate analysis and a multivariate logistic regression model.

Results: This study included 6,712 women who were pregnant with a singleton foetus, including 460 (6.85%, 95% CI: 6.27, 7.48) women who conceived with assistance. Women who conceived with assistance were more likely to be older ($p < 0.001$), nulliparous ($p < 0.001$), who had a higher prevalence of obesity ($p < 0.001$), pre-gestational diabetes mellitus ($p = 0.009$), gestational diabetes ($p < 0.001$) and pre-pregnancy hypothyroidism ($p < 0.001$) in this population. Assisted conceptions were not significantly associated with small for gestational age babies ($p = 0.09$), still births ($p = 0.56$), or neonatal deaths ($p = 0.89$). Assisted conceptions were associated with a higher incidence of caesarean sections (adjusted OR: 1.37, 95% CI: 1.11-1.70) in a multivariate logistic regression model.

Conclusion: After adjusting for differences in maternal characteristics, pregnant women with singleton foetuses, who conceived with assistance, had similar outcomes, except for higher caesarean section rates, as compared to women who conceived naturally.

Keywords: Assisted Conception, Natural conception, Outcomes, Pregnancy, Singleton

INTRODUCTION

An estimated 60-80 million couples are considered to be infertile, based on the World Health Organization (WHO) estimates, who include 3 to 5% of couples who are infertile due to unknown or unpreventable conditions [1]. Primary infertility is defined by the WHO as the inability to conceive within two years of exposure to pregnancy (sexually active, not using contraceptives, non-lactating) among women who are aged 15 to 49 years and secondary infertility is defined as the inability to conceive, following a previous pregnancy [2,3]. Studies have estimated childlessness to be nearly 5.5% in women who are aged 30 to 49 years and to be 5.2% in women who are aged 45 to 49 years in India [4]. In absolute numbers, there may be an estimated 4.9 million women in India who are infertile [4]. If we add secondary infertility to these estimates, the number of infertile couples in India may rise to 17.9 million [4]. The WHO estimated the overall prevalence of primary infertility in India to range from 3.9 to 16.8% [1] and it estimated 5% primary infertility in the state of Andhra Pradesh in south India [5]. A decline in total fertility rate (TFR) among women who are aged 15 to 49 years in urban India, from 2.70 in the National Family Health Survey (NFHS)-I to 2.06 in the NFHS-III, has been reported [6]. The TFR for the state of Andhra Pradesh for urban populations declined from 2.35 in NFHS-I to 1.73 in NFHS-III [6]. The TFR for rural India declined from 3.67 in NFHS-I to 2.69 in NFHS-III and that for Andhra Pradesh declined from 2.67 in NFHS-I to 1.82 in NFHS-III [6].

The use of assisted conception services, both for medical reasons, as well as part of planned family approach, where the partners live

apart, is being increasingly recognized as a viable reproductive option in India. Several studies have reported that outcomes of pregnancy were worse in assisted conceptions as compared to those in natural conceptions, which were primarily related to the larger incidences of multiple pregnancies with assisted conceptions [7,8]. In this study, we aimed to compare the perinatal outcomes of pregnancies in singleton mothers, which were stratified by the type of conception.

MATERIALS AND METHODS

A retrospective study design and a data collection protocol that adhered to the tenets of the Declaration of Helsinki were used to collect information on pregnant women with singleton foetuses, who delivered at gestation ages of ≥ 24 weeks at the study institute in the year 2012. Women with multiple pregnancies and those who delivered earlier than 24 gestation weeks were excluded. Details of pregnancy, including demographic details, prior and current obstetric, medical and surgical histories, details of personal risk behaviours, family histories, types of conception, details of clinical exams and laboratory investigations as part of antenatal care, trimester specific ultrasound examinations and foetal growth assessments, details of delivery and post-partum period were entered in medical records, that were transcribed to an electronic database. Women were assessed for height and weight at baseline and a baseline body mass index was derived. Thyroid disorders were screened for at baseline through a universal screening protocol. We defined gestational diabetes, based on the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria [9].

Characteristic	Natural Conception (n=6,252)	Assisted Conception (n=460)	p-Value
Mean Maternal Age (SD)	27.43 (3.93)	28.64 (4.94)	<0.001
Maternal Age >35 years	188 (3.01%)	32 (6.96%)	<0.001
Nulliparous	3,482 (55.69%)	386 (83.91%)	<0.001
Primigravid	2,796 (44.72%)	294 (63.91%)	<0.001
Body Mass Index >30	1,250 (19.99%)	126 (27.39%)	<0.001
Gestational Hypertension	241 (3.85%)	24 (5.22%)	0.14
Pre-eclampsia	286 (4.57%)	25 (5.43%)	0.40
Eclampsia	18 (0.29%)	0 (0.00%)	0.25
Chronic Hypertension	97 (1.55%)	9 (1.96%)	0.50
Pre-gestational diabetes mellitus	92 (1.47%)	14 (3.04%)	0.009
Gestational diabetes mellitus	1,009 (16.14%)	134 (29.13%)	<0.001
Screen positive hypothyroid	428 (6.25%)	31 (6.74%)	0.93
Pre-pregnancy hypothyroid	614 (9.82%)	77 (16.74%)	<0.001

[Table/Fig-1]: Characteristics of the study population stratified by type of conception

Outcome	Natural Conception n	Assisted Conception n	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
All preterm births <37 gestation weeks	906	85	1.40 (1.09, 1.80)	1.27 (0.98, 1.65)
Gestational age 32-36 weeks	734	70	1.36 (1.04, 1.77)	1.24 (0.94, 1.64)
Gestational age <32 weeks	172	15	1.24 (0.72, 2.13)	1.11 (0.63, 1.92)
Birth weight 1500-2499 grams	808	80	1.42 (1.10, 1.83)	1.36 (1.05, 1.76)
Birth weight <1500 grams	217	16	1.00 (0.60, 1.68)	0.85 (0.50, 1.44)
Small for gestational age	630	57	1.28 (0.96, 1.72)	1.23 (0.91, 1.66)
Caesarean section	2,691	244	1.56 (1.27, 1.91)	1.37 (1.11, 1.70)
Still born	76	7	1.26 (0.58, 2.74)	1.08 (0.48, 2.39)
Neonatal deaths	44	3	0.93 (0.29, 2.99)	1.00 (0.30, 3.33)

[Table/Fig-2]: Outcomes of pregnancy stratified by type of conception
* Adjusted for maternal age, nulliparity, body mass index, pre-gestational and gestational diabetes mellitus, and pre-pregnancy hypothyroidism

Pregnancy induced hypertension was defined by using the criteria which was developed by the International Society for the Study of Hypertension in Pregnancy and it included proteinuria as a criteria [10].

The details of labour and delivery, including gestational age at delivery, type of labour-induced or spontaneous, mode of delivery, and obstetric complications were recorded. The details of the baby, including neonatal morbidity and mortality, NICU admission, APGAR scores, still born status and intrauterine foetal deaths were recorded.

Assisted conception was considered to include all invasive and non-invasive methods like OI, IUI, IVF, ICSI. Primary infertility is defined, for clinical purposes, as the inability to conceive within two years of

exposure to pregnancy (sexually active, not using contraceptives, non-lactating) among women who are aged 15 to 49 years.

The data was initially entered into a Microsoft Excel spreadsheet and it was then exported to SPSS statistical software (version 14.0) for statistical analysis. The primary outcome of interest was preterm births that were defined as a spontaneous onset of labour and those with preterm rupture of the membranes, which occurred before 37 completed gestation weeks. The data was initially explored for normality of distribution by using measures like skewness and kurtosis, as well as the Shapiro Wilk test for Normality. The frequency distribution, point estimates and 95% CI around point estimates were determined. Bivariate analysis was done by using One Way Analysis of Variance (ANOVA) test for continuous variables and Chi-square or Fisher's Exact test for categorical variables. A univariate logistic regression model was used to determine odds ratios and the 95% confidence intervals for outcomes which were associated with exposure. Factors that were significantly different between the two groups were further assessed by using a multivariate logistic regression model. We considered a p value of <0.05 as statistically significant for this study.

RESULTS

This study included 6,712 women who were pregnant with singleton fetuses, who delivered at the study institute in the year 2012. Four hundred and sixty (6.85%, 95% CI: 6.27, 7.48) women in the study population conceived with assistance. Methods of assistance included OI (n=283), IVF (n=99), IUI (n=72) and ICSI (n=10). The characteristics of the study population, which were stratified by conception, have been presented in [Table/Fig-1].

On bivariate analysis, assisted conceptions were significantly associated with preterm gestations of < 37 weeks (p=0.009). On further exploration of preterm births by using bivariate analysis, assisted conceptions were significantly associated with preterm births at 32-36 gestation weeks (p=0.02) but not with preterm births at < 32 gestation weeks (p=0.43). Birth weights of < 1,500 grams (p=0.99) were not significantly associated with assisted conceptions; however, birth weights which were between 1,500 and 2,499 grams (p=0.006) were significantly associated with assisted conceptions on bivariate analysis. Assisted conceptions were not significantly associated with small for gestational age babies (p=0.09), still births (p=0.56), or neonatal deaths (p=0.89). Birth weight (1,500-2,499 grams) and caesarean sections were significantly associated with assisted conceptions after adjusting for maternal age, body mass index, parity, pre-gestational and gestational diabetes, and pre-pregnancy hypothyroidism [Table/Fig-2]. Birth weights should be lower in babies who are delivered at earlier gestation weeks (preterm deliveries). The association of birth weight (1,500-2,499 grams) with assisted conceptions, which was explored further by adding gestational age at delivery to the multivariate logistic regression model, showed that birth weights (1,500-2,499 grams) were not significantly associated with assisted conceptions (adjusted OR: 1.12, 95% CI: 0.81, 1.55).

The results were further explored and stratified, based on type of assisted conception. OI was not associated with gestational age at delivery of <32 weeks (p=0.55), gestational age at delivery of 32-36 weeks (p=0.52) or birth weights of < 1500 grams (p=0.56), small for gestational age babies (p=0.06), caesarean sections (p=0.71) or still born babies (p=0.19) in the regression model. IUI was not associated with gestational age at delivery of <32 weeks (p=0.34), gestational age at delivery of 32-36 weeks (p=0.85) or birth weights of < 1500 grams (p=0.60), small for gestational age babies (p=0.51), or caesarean sections (p=0.38) in the regression model. IVF was associated with gestational age at delivery of <32 weeks (p=0.02), gestational age at delivery of 32-36 weeks (p=0.001) and caesarean sections (p<0.001), but it was not associated with birth weights of < 1500 grams (p=0.38), small for gestational age babies (p=0.53) or still born babies (p=0.92) in the regression model.

DISCUSSION

Assisted conceptions were associated with preterm gestations, mild low birth weights and an increased incidence of caesarean sections, but they were not associated with small for gestational age babies and perinatal mortality on bivariate analysis. The results of this study indicated that women who conceived with assistance were older or nulliparous, with a higher prevalence of morbidity, like obesity (body mass index >30), pre-gestational diabetes mellitus, gestational diabetes and pre-pregnancy hypothyroidism as compared to women who conceived naturally in this population. The difference in maternal characteristics between women who conceived naturally and with assistance is important, as these characteristics can act as confounders that affect perinatal outcomes. After adjusting for these differences in maternal characteristics, assisted conceptions were associated only with a higher incidence of caesarean sections.

Several studies worldwide have reported differing results for associations of adverse perinatal events with assisted conceptions, although they are limited by a lack of adequate power to determine associations with reasonable accuracy [11-18]. Several of these studies were limited by a lack of adequate power to determine associations with reasonable accuracy. A systematic review of controlled studies on assisted conceptions reported an increased incidence of adverse perinatal events- preterm deliveries (pooled relative risk 2.04, 95% CI: 1.80-2.32), low birth weight babies (pooled relative risk 1.70, 95% CI: 1.50-1.92), caesarean sections (pooled relative risk 1.27, 95% CI: 1.16-1.40), small for gestational age babies (pooled relative risk 1.54, 95% CI: 1.44-1.66) and perinatal mortality (pooled relative risk 1.68, 95% CI: 1.11-2.55)-with assisted conceptions [19].

Several of these reported associations are inter-linked, which include caesarean sections for preterm deliveries or planned interventions for small for gestational age babies, and consequent lower birth weights of the babies, with an increased risk for morbidity and mortality. We found that the association between preterm delivery and low birth weight were no longer significant, after adjusting for these confounding factors. Preterm delivery of a baby may be spontaneous or it may be a planned decision which is based on the health of the mother and/or the foetus, including suspicion of foetal compromise. Obstetricians may be more cautious with assisted conceptions, considering the difficulties that women have in conception, the relatively older ages, nulliparous status, associated medical co-morbidities and the relative importance of such pregnancies and they may tend to deliver the babies by using planned elective procedures if there is any suspicion of foetal or maternal distress. The availability of neonatal services (neonatal intensive care units and nurseries) has improved outcomes of preterm deliveries, including very preterm deliveries, thus making the decisions for planned preterm deliveries more feasible. Unfortunately, we could not distinguish between planned preterm and spontaneous preterm deliveries with reasonable accuracy in this study; a prospective study design will help us in making that distinction.

The documentation and the retrospective cohort study design may be considered as strengths of this study. However, it does have

several limitations. It was done at a single tertiary care centre. While the single centre nature of this study offers advantages in terms of standardized procedures and documentations, it does have a limitation in terms of representativeness of the population and hence, in terms of generalizability of the results to a larger population. In conclusion, the results of this study indicate that women with assisted conceptions do not have significantly different perinatal outcomes as compared to natural conceptions in singleton pregnancies, if we adjust for the difference in maternal characteristics. Women with assisted conceptions tend to have higher rates of caesarean sections, probably as part of a planned obstetric approach that minimizes risk to the foetus and mother and intervenes on the side of caution. Further studies are required to determine as to whether the rates of caesarean sections can be reduced with more term vaginal deliveries in women with singleton foetuses, after undergoing assisted conceptions.

REFERENCES

- [1] Infecundity, infertility, and childlessness in developing countries. DHS Comparative Reports No 9. Calverton, Maryland, USA: ORC Macro and the World Health Organization; 2004.
- [2] Reproductive health indicators for global monitoring: Report of the second interagency meeting, 2001. Geneva: World Health Organization.
- [3] Inhorn MC. Global infertility and the globalization of new reproductive technologies: illustrations from Egypt. *Soc Sci Med*. 2003; 56:1837-51.
- [4] Shivaraya M, Halemani B. Infertility: psycho-social consequence of infertility on women in India. *Indian Journal of Social Development*. 2007;7(2):309-16.
- [5] Unisa S. Childlessness in Andhra Pradesh, India: Treatment-seeking and consequences. *Reprod Health Matters*. 1999;7:54-64.
- [6] International Institute for Population Sciences (IIPS) and Macro International. National Family Health Survey (NFHS-3), 2005-06: India: Volume I. Mumbai: IIPS. 2007.
- [7] Dhont M, De Sutter P, Ruysinck G, Martens G, Bekaert A. Perinatal outcome of pregnancies after assisted reproduction: a case-control study. *Am J Obstet Gynecol*. 1999;181:688-95.
- [8] Australian In Vitro Fertilisation Collaborative Group. High incidence of preterm births and early losses in pregnancy after in vitro fertilisation. *BMJ*. 1985;291:1160-3.
- [9] International Association of Diabetes and Pregnancy Study Groups. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33: 676-82
- [10] Davey DA, Mac Gillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 1988; 158: 892-8
- [11] Koudstaal J, Braat DD, Bruinse HW, Naaktgeboren N, Vermeiden JP, Visser GH. Obstetric outcome of singleton pregnancies after IVF: a matched control study in four Dutch university hospitals. *Hum Reprod*. 2000;15:1819-25.
- [12] Dhont M, De Neubourg F, van der Elst J, De Sutter P. Perinatal outcome of pregnancies after assisted reproduction: a case-control study. *J Assist Reprod Genet*. 1997;14:575-80.
- [13] Isaksson R, Gissler M, Tiitinen A. Obstetric outcome among women with unexplained infertility after IVF: a matched case-control study. *Hum Reprod*. 2002;17:1755-61.
- [14] Maman E, Lunenfeld E, Levy A, Vardi H, Potashnik G. Obstetric outcome of singleton pregnancies conceived by in vitro fertilization and ovulation induction compared with those conceived spontaneously. *Fertil Steril*. 1998;70:240-5.
- [15] Pandian Z, Bhattacharya S, Templeton A. Review of unexplained infertility and obstetric outcome: a 10 year review. *Hum Reprod*. 2001;16:2593-7.
- [16] Tanbo T, Dale PO, Lunde O, Moe N, Abyholm T. Obstetric outcome in singleton pregnancies after assisted reproduction. *Obstet Gynecol*. 1995;86:188-92.
- [17] Verlaenen H, Cammu H, Derde MP, Amy JJ. Singleton pregnancy after in vitro fertilization: expectations and outcome. *Obstet Gynecol*. 1995;86:906-10.
- [18] Reubinoff BE, Samueloff A, Ben Haim M, Friedler S, Schenker JG, Lewin A. Is the obstetric outcome of in vitro fertilized singleton gestations different from natural ones? A controlled study. *Fertil Steril*. 1997;67:1077-83.
- [19] Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ*. 2004; Jan 31;328(7434):261.

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