International Journal Dental and Medical Sciences Research
Volume 5, Issue 2, Mar - Apr 2023 pp 102-109 www.ijdmsrjournal.com ISSN: 2582-6018

Comparison Of Maternal Outcomes Of Pregnancy And Perinatal Outcomes In Patients Aged Above 35 Years Following Assisted Reproductive Technology And Spontaneous Conceptions.

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Date of Submission: 01-03-2023 Date of Acceptance: 10-03-2023

ABSTRACT:
Background: Assistedreproductive technology (ART)despite its success, has a higher risk of adverse neonatal and peri-natal outcomes compared to spontaneous conception, even when limited to singleton births. We conducted this study to observe the outcomes and risks of ART in the South Indian populationwhen compared to spontaneous conceptions in patients with maternal age of ≥ 35 years.
Materials and Methods: The objective of the present study was to review the maternal outcomes and perinatal complications in pregnancy in patients aged more than 35 years conceived by ART and by spontaneous conception.A retrospective cohort study was doneat our institute, studyincluded patients delivered at our institutebetween May 2017to April 2021, atotal of 272patients ≥ 35 years of agewho conceived by Assisted Reproductive Technology (ART group) (n=127)andwith spontaneous conception (n=146) were included in the study.
Results: This retrospective cohort study conducted at our institutefound more incidence of antenatal, perinatalcomplications in the ART group when compared to the spontaneous conceptiongroup. The incidence of poor neonatal outcomes was also found to be marginally higher.
Keywords: Assisted Reproductive Technology (ART), Peri-natal complications, multiple pregnancy, spontaneous conception, In-vitro Fertilization (IVF).

I. INTRODUCTION:

With advances in technology and provision of services, an increasing number of infants are born as a result ofAssisted Reproductive Technology (ART) [1].Women conceived by ART were at increased risks of several adverse pregnancy outcomes compared with women conceived naturally. Multiple pregnancies due to multiple embryos transferred could partly explain the increased risks. A "good perinatal outcome" after ART is the live birth of a singleton infant at term (at ≥ 37 completed weeks of gestation) and at a normal birth weight (≥ 2,500 g) [2]. Despite itsability to overcome infertility, there is a concern regarding ART on its safety and effect on maternal and child health. It has been well documented that ART pregnancies have a significantly higher risk of multiple pregnancies and adverse perinatal outcomes (that include preterm delivery, low birth weight, and birth defects)[3-5]. Some studies have also suggested an increased risk of preeclampsia, gestational hypertension, placenta previa, and gestational diabetes in ART pregnancies[6-8].

Previous studies reported that pregnancies following ART have a higher risk of adverse neonatal outcomes, including preterm delivery, low birth weight, birth defects, and perinatal mortality [9-11] when compared to spontaneous conception, even when limited to singleton births [9, 11, 12]. Potential reasons for the poorer perinatal health of ART mothers and children have been related to procedures involving ART, such as medicines used, altered hormonal environment at the time of implantation, and the manipulation of gametes and embryos or a combination of these [13, 14].Data from two meta-analyses have confirmed that ART involving in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) was associated with an increased risk of adverse perinatal outcomes [11, 15].

It has also been suggested that the worse health in infants born is due mainly to the higher risk incidence of multiple pregnancies and not related to ART procedures [17, 18]. On the whole, most of the previous estimates of potential adverse health outcomes among ART pregnancies have been based on studies from high-income countries. So, we aimed to observe the potential adverse outcomes among ART pregnancies in the South Indian population.

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II. MATERIALS AND METHODS:

Study Design:

This retrospective cohort studywas carried out to explore associations between assisted reproductive technology (ART) and maternal and neonatal outcomes in a total of 272patients 127cases (ART) and 146 controls (spontaneous conception). Women above 35 years of age conceived byAssisted Reproductive Technology (ART)and women conceived by spontaneous conception who were delivered at the Institute of Reproductive Medicine (IRM) of Madras MedicalMission (MMM)Hospital Chennai between May 2017 and April 2021were included in this study. The study was approved by the Ethics Committee (EC) of the institution.

Monitoring Procedures:

The antenatal check-ups were performed routinely from theday of early pregnancy. The routine CBC (Complete Blood Count), beta-HCG (human Chorionic Gonadotrophin), early Pregnancy Viability scan andNuchal Translucency (NT) scans were performed. Double marker and other all investigations were carried out according to the protocol. Anomaly scans and regular growth scans were also performed to check the growth of the foetus. Patients were admitted at 38 weeks for induction or elective LSCS, when the stages of labour failed to progress emergency Caesareansections were done as per protocol.

Complications:

The complications like gestational diabetes, gestational hypertension,pre-eclampsia, and anaemiaduringthe pregnancy period were monitored and treated as per the standard protocols. The perinatal complications like Placental abruptions,preterm delivery,premature rupture of membranes(PROM),polyhydramnios,oligohydramnios, preterm labour,and low birth weight,werecompared among each agegroup.

Outcomes:

Maternal health outcomes included mode of delivery (caesarean/vaginal); pregnancy complications (gestational hypertension,gestational diabetes, pre-eclampsia)were extracted from medical records.

Antenatal complications between each group such as anaemia during pregnancy, elective and emergency caesarean section were recorded.

Perinatal complications like placenta previa, placentalabruptions, premature rupture of membranes, post-partumhaemorrhage, polyhydramnios and oligohydramnios were recorded, The number of pre-term labour, low birth weight, foetal macrosomia, small for date infants& infants with congenital anomalies were recorded.

The number of offspring delivered (single or multiple pregnancies) were recorded.

Statistical Analysis:

The categorical variables such as age groups, pregnancy and perinatal complications, mode of conception and delivery and pregnancy outcomes were expressed in numbers (n) and percentages (%). The descriptive analysis of the variables was performed using Microsoft Excel. All the data were double-checked for errors.

III. RESULTS:

Over 4years of study, 272women (age≥ 35 years) delivered and among them 127 were ART conceptions,146 wereSpontaneous conceptions.The study period was between May 2017 to April 2021. The cases were classified into four groups as shown in Table 1. Women in the range of 35-37 years of age group were predominant in both cases and controls. Antenatal, perinatal, and outcomes of pregnancy were analysed.

Table. 1 Age Distribution

Group	**Age Range (In years)**	**No. of Patients, cases** n (%) (n=127)	**No. of Patients, controls** n (%) (n=146)
1	35-37	68 (53)	110
2	38-40	39 (31)	36
3	41-45	15 (12)	0
4	>45	5 (4)	0

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Table. 2 Antenatal and Perinatal complications

Antenatal Complications	**Age group (in years) ART PREGNANCIES (IUI+FER)**				**Total,** n=127 (%) **ART PREGNANCIES**	**Spontaneous conception (Total n=146)**
	35-37	**38-40**	**41-45**	**>45**		
Gestational Hypertension	08	13	-	-	21(17 %)	6 (3.6%)
Gestational Diabetes	21	26	05	02	53 (41%)	10(6.5%)
Hypothyroidism	34	16	03	-	53 (41%)	-
Pre-eclampsia	4	2	1	1	8(5.9%)	4(2.1%)
Other Complications						
Fibroids	-	2	-	-	2	1
Endometriosis	1	-	-	-	1	1
Anaemia	1	-	-	-	17	16
Asthma	1	1	-	-	2	7
Rheumatic Heart Disease	-	1	0	-	-	-
Perinatal Complications						
Placenta Previa	4	2	1	1	8(6%)	5(3.4%)
Placental abruption	2	1	0	0	2(1.5%)	0
Premature rupture of membranes	9	4			13(9.8%)	5(3.3%)
Postpartum haemorrhage					10(7.5%)	4(2.9%)
Oligohydramnios	03	-	-	-	03(3.81%)	9(6.5%)
Polyhydramnios	02	-	-	-	02(2.54%)	2(1.4%)

Table.3 Outcomes of Pregnancy

Pregnancy Outcomes	**Age group (in years)**				**Total,** n (%) ART	Total SPONTANEOUS **n (%)**
	35-37	**38-40**	**41-45**	**>45**		
Twin Pregnancy	14	20	02	-	36 (14.17)	3(2%)
Birth Weight > 2.5	106	90	18	10	244 (85.9)	138(94%)
Birth Weight <2.5	12	28	-	-	40 (14.08)	8(6%)
Abortion	02	-	-	-	02 (0.6)	2(1%)
Infants with Congenital Anomalies	0	0	-	-	0	0
Still Birth	02	-	-	-	02 (0.6)	1

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Table 4 Neonatal outcomes

	35-37	**38-40**	**41-45**	**>45**	TOTAL ART(n=127)	TOTAL SPONTANEOUS(n=146)
Pre-term labour, &	25	10	10	5	50(40%)	15(10.5%)
Infants with low APGAR score	2	2	1	1	5(4.35%)	4(3.0%)
Foetal macrosomia	2	2	0	0	4(3.3%)	10(7.2%)
Small for date infants					5(3.8%)	2(1.2%)

Figure. 1 Prevalence ofHypertension and Diabetes and pre-eclampsiain ART and spontaneous conception

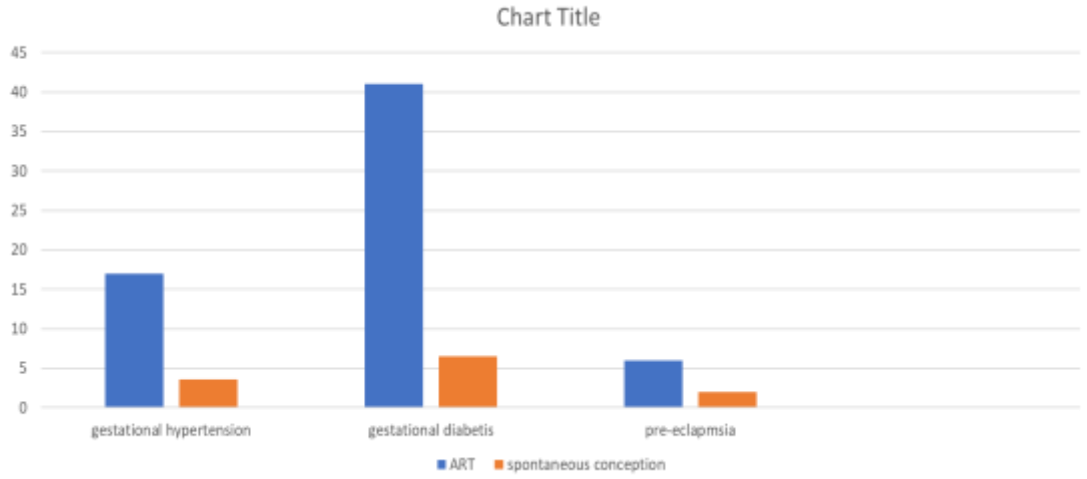
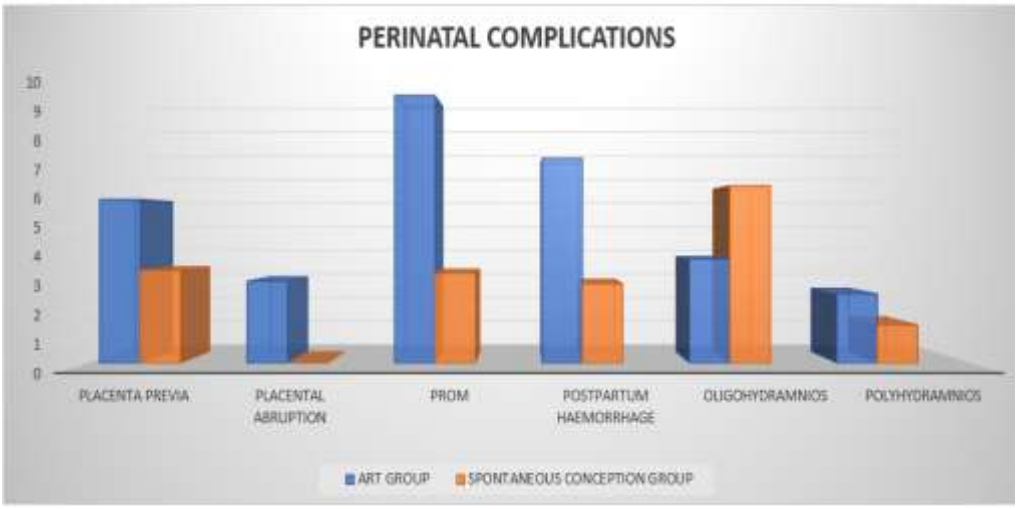


Figure 2 Perinatal complication of pregnancy.



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Volume 5, Issue 2, Mar - Apr 2023 pp 102-109 www.ijdmsrjournal.com ISSN: 2582-6018

Figure 3 Neonatal complications

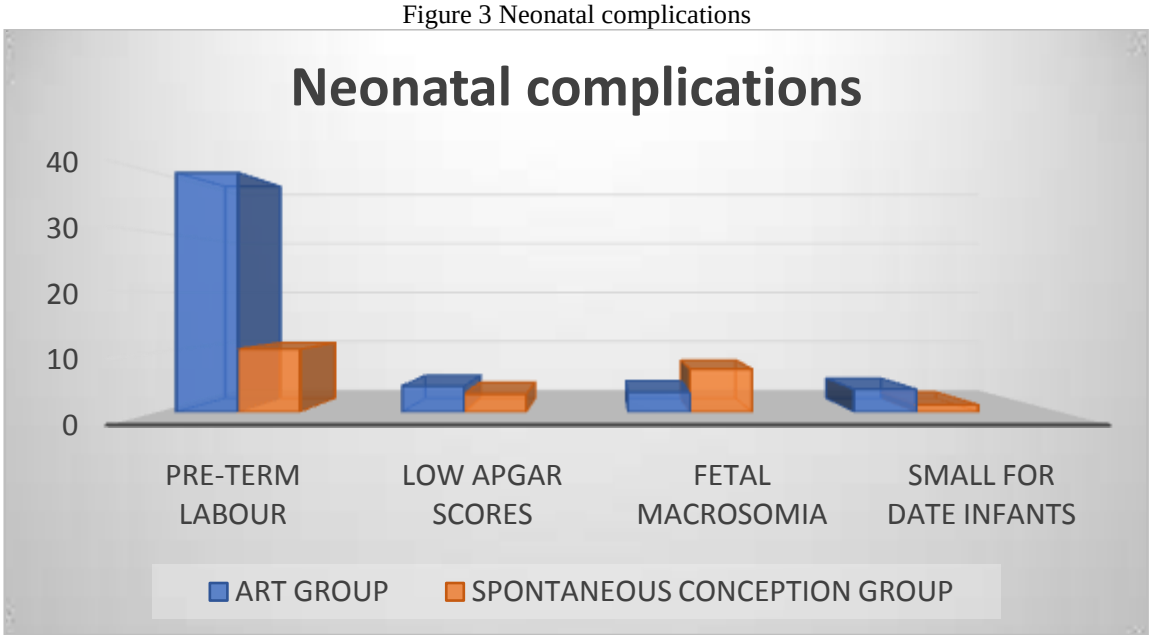

Table. 3 Mode of Delivery and Conception

		Age group (in years)				**Total,** n=127(100%)	**Total spontaneous** n=146(100%)
		35-37	**38-40**	**41-45**	**>45**		
1.	**Mode of Delivery:**						98(67.2%)
	Normal	01	-	-	-	2(1.6%)	48(32.8%)
	Caesarean	66	39	15	05	125(98.4%)	8(5.5%)
	• Emergency	04	04	-	-	8 (6.3%)	
							40(27.4%)
	• **Elective**	62	35	15	05	117(83.6%)	
2.	**Mode of Conception**						
	FER(Frozen embryo replacement)	20	21	03	05	52 (40.9%)	-
	IUI(Intrauterine insemination)	03	-	-	-	03 (3.8%)	
		40	33	02	-	75(59.05%)	

Hypothyroidism was observed in 41% of cases and in 5 % of the controls. Diabetes was found in 41% (58% gestational diabetes and 42 %overt diabetes)of the cases and in 6.5% of the controls. Hypertension was present in 17% of cases (PIH in 58%, Chronic Hypertension in 47% and impending eclampsia in 14%) and in 3.6% of the controls.

Normal deliveries were 13.3 % and 86.6% were caesarean deliveries (elective caesarean: 56% and emergency caesarean: 43%) in the ART group while spontaneous conception group 67% of the deliveries were normal vaginal and 33% were caesarean section.Birth weight of more than 2.5 kg was observed in 86% and lessthan 2.5kg in 14% ofnew-bornsin the ART group and 94% of the new-borns in the spontaneous conceptions group weighed more than 2.5 kg and 6% below 2.5 kg. Stillbirthin 0.6% of babies was observed in ART group.

Perinatal complications like Placenta Previawere found in 6% of the ART group and 3.4 % of the spontaneous conception group.Placental abruption was found in 1.5 % of the cases in the

ART group andno cases in the spontaneous conception group. Premature rupture of membranes was found in 9.8% of the 3.3% of the spontaneous conception group. Postpartumhaemorrhage was found in 7.5% of the ART group and 2.9% of the spontaneous conception group. Polyhydramnioswas found in2.54 % of the ART group and 1.4% of the spontaneous conception group.Oligohydramnios was found in3.81 percent of the ART group and 6.5% of the spontaneous conception group. Preterm labour was more prevalent in the ART group and small for age infants and infants with low 1 minute Apgar score were more prevalent in the ART group.

IV. DISCUSSION:

Although ART procedures have helped many women to overcome infertility, the concern is growing regarding the possible negative effects of these procedures on maternal and child health. In this paper, we have compared maternal and neonatal outcomes after ART technologies relative to natural conception in South Indian Population. Several studies have been performed to address this issue. While some studies have reported that ART pregnancies compared with those conceived naturally, whether singleton or multiple, have an increased risk of maternal complications [11, 19, 20] and a higher risk of preterm birth, low birth weight, birth defects, malformations, and perinatal mortality [14, 21], in contrast, other studies have shown that these outcomes are similar between ART and spontaneous conception [22, 23].

Although success with ART treatment is surely associated with the number of embryos transferred, a higher number of embryos transferred has been strongly associated with adverse perinatal outcomes such as preterm birth and low birth weight[24, 25].

The transfer of single embryo of high quality should be promoted. However, ART singleton pregnancy still showed higher risks of several adverse pregnancy outcomes compared with naturally pregnancy, suggesting ART itself is also significantly correlated with pathological pregnancy. Therefore, policies related to ART indications should be strictly formulated to reverse the high rate of ART pregnancy. Given our findings, prenatal and intrapartum monitoring should be strengthened, and neonatal outcomes should be closely observed for ART pregnancy.

Since 1998 the Society for Assisted Reproductive Technology (SART) and American Society for Reproductive Medicine (ASRM) has published updated guidelines to assist ART programs and patients in determining the appropriate limit to the number of cleavage-stage embryos or blastocysts to transfer, aiming to promote singleton gestations, reduce twin gestation, and eliminate high-order multiple gestations [26]. A policy of single-embryo transfer in stimulated cycles becomes more popular and is currently the most effective measure to reduce the incidence of multiple pregnancies [27].

In our study, even though the ART involved single-embryo transfer in all cases, outcomes of multiple pregnancies were observed in 14 % (n=36) of the cases. With the increasing implementation of a policy of single-transfer embryos, multiple pregnancies have reduced dramatically [28], but is still an outcome of ART that is undesirable.

V. CONCLUSION:

While there seems to be a higher risk of adverse perinatal outcomes with some of the ART procedures,the absolute risk increase is generally low. It is important for clinicians to have this knowledge to better counsel and care for their patientsin cases with high-risk pregnancies, good outcomes can be achieved by the provision of standardized and good ante-natal, intra-natal and post-natal careto avoid pregnancy and perinatal complications in ART therapy.

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