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Outcome Of Pregnancies Conceived with IVF and ICSI Depending on Age Factor

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Abstract

Infertility, a reproductive health condition prevalent among one in every four couples in the developing countries, is a neglected problem. In this era of exponential industrialization and global changes, lifestyle disorders like infertility are on the rise. It is estimated that infertility affects 8 to 12 per cent of couples worldwide. overall IVF pregnancies are often seen as risky mainly due to multiple gestations. However, even singleton ART pregnancies are associated with increased incidences of preterm birth, low birth weight, small-for-gestational-age (SGA) infants, and obstetric complications such as preeclampsia, placental abruption, and placenta previa. While there are many studies that compare pregnancies after assisted reproductive techniques with spontaneously conceived pregnancies, fewer data are available that evaluate the differences between IVF and ICSI-conceived pregnancies. The aim of our study was to compare adverse pregnancy outcomes in IVF and ICSI cases and how they vary depending on age factor. This retrospective cohort study was conducted at Radhakrishna multispecialty hospital and IVF center, Bangalore during January 2013 to January 2019. A total of 667 of which 434 were IVF and 233 ICSI cases were done. 263 cases were pregnancy positive out of which 149cases underwent conventional IVF and 114 cases underwent ICSI. These cases were divided into three groups depending upon age factor. Outcome variables included maternal parameters: i.e., age; gravity; duration of infertility, pregnancy complications such as abortions, ectopic pregnancy, multiple pregnancies, pregnancy-induced hypertension, preeclampsia, premature rupture of membranes, gestational diabetes mellitus, IUGR and preterm labour; antepartum hemorrhage and fetal parameters: i.e., gestational age; low and very low birth weight, meconium aspiration syndrome and need for NICU admission. In the study among those who had IVF pregnancy, there was no significant association between causes and Age distribution. however, a greater number of ICSI cases were done for male factor infertility. In IVF group, there was significant difference in Biochemical Pregnancy, Gestational DM, Pre-Term Labour, Oligo Hydramnios and Poly Hydramnios with respect to age distribution. I.e., all the above-mentioned complications were significantly high in mothers in the age group 30 to 40 years compared to other age groups. There was no significant difference in other complications with respect to age distribution. In ICSI group, there was significant difference in Biochemical Pregnancy with respect to age distribution. I.e., Biochemical Pregnancy were significantly high in mothers in the age group 30 to 40 years compared to other age groups. In the study there was significant difference in Preterm birth and NICU admission in IVF group with respect to age distribution. I.e., Preterm birth and NICU admission were highest in the age group 30 to 40 years mother. Women who conceived with IVF and ICSI were at higher risk of maternal and perinatal complications particularly with age group 30-40 years. There was significant increase in multiple pregnancies, gestational diabetes and preterm labour and NICU admission in IVF group. Hence with proper diagnosis, stimulation protocol and with single embryo transfer can reduce the risk of multiple birth and further perinatal complications.

Keywords: *experience, youth, menstruation.*

Introduction

Infertility, a reproductive health condition prevalent among one in every four couples in the developing countries, is a neglected problem. In this era of exponential industrialization and global changes, lifestyle disorders like infertility are on the rise. It is estimated that infertility affects 8 to 12 per cent of couples worldwide [1]. In India, the overall prevalence of primary infertility varies from 3.9 to 16.8 per cent.[2]. Assisted reproductive technologies (ART) such as in vitro fertilization (IVF)and intracytoplasmic sperm injection (ICSI) have emerged as a promising treatment option for infertility. The obvious goals of all such treatments are to achieve a pregnancy and subsequent birth of a healthy infant, but overall IVF pregnancies are often seen as risky mainly due to multiple gestations. However, even singleton ART pregnancies are associated with increased incidences of preterm birth, low birth weight, small-for-gestational-age (SGA) infants, and obstetric complications such as preeclampsia, placental abruption, and placenta praevia.[3][4] While there are many studies that compare pregnancies after assisted reproductive techniques with spontaneously conceived pregnancies, fewer data are available that evaluate the differences between IVF and ICSI-conceived pregnancies. The aim of our study was to compare adverse pregnancy outcomes in IVF and ICSI cases and how they vary depending on age factor.

Materials and Methods

This retrospective cohort study was conducted at Radhakrishna multispecialty hospital and IVF center, Bangalore during January 2013 to January 2019. A total of 667 of which 434 were IVF and 233 ICSI cases were done. 263 cases were pregnancy positive out of which 149cases underwent conventional IVF and 114 cases underwent ICSI. These cases were divided into three groups depending upon age factor. Patients who were used donor egg/ semen / embryo were excluded from the study group. The etiology in each case was diagnosed with ultrasonography, laboratory parameters, hysterolaparoscopy (when appropriate) and sperm analysis was done in all couples. Unexplained infertility was defined as infertility lasting at least one year for which no explanatory factor was identified. The pregnancies and deliveries of the study and reference groups were handled in the same hospital, and ART treatments were carried out in the same unit.

Outcome variables included maternal parameters: i.e., age; gravity; duration of infertility, pregnancy complications such as abortions, ectopic pregnancy, multiple pregnancies, pregnancy- induced hypertension, preeclampsia, premature rupture of membranes, gestational diabetes mellitus, IUGR and preterm labour;antepartum hemorrhage and fetal parameters: i.e., gestational age; low and very low birth weight, meconium aspiration syndrome and need for NICU admission.

Statistical analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram.

p value (Probability that the result is true) of <0>

Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data. [5][6]

Results

total of 667 patients underwent IVF/ICSI during six-year period between January 2013 to January 2019. Out of these cases pregnancy positive were 263. Of them 63%(149cases) by IVF and 43.3% (114 cases) by ICSI. In the study among subjects in the age group 20 to 30 years, 57.7% had pregnancy by IVF and 49.1% by ICSI. Among subjects in the age group 30 to 40 years, 39.5% had pregnancy by IVF and 44.7% by ICSI. There was no significant association between age and type of pregnancy.

Table 1: Characteristic of Participants

Age	IVF Group (149)	ICSI Group (114)
20-30	*86 (57.7%)*	*56 (49.1%)*
30-40	*59 (39.5%)*	*51 (44.7%)*
>40	*4 (2.68%)*	*7 (6.14%)*

χ 2 =3.136, df =2, p =0.208

Duration of Infertility with respect to age distribution in IVF and ICSI group

Age (Years)	IVF			ICSI		
	20-30 (n=86)	***30-40 (n=59)***	***>40 (n=4)***	***20-30 (n=56)***	***30-40 (n=51)***	***>40 (n=7)***
<5	*24*	*10*	*0*	*16*	*16*	*1*
5-10	*52*	*40*	*2*	*32*	*26*	*3*
>10	*10*	*9*	*2*	*8*	*9*	*3*
Total	*86*	*59*	*4*	*56*	*51*	*7*
P value		*0.122*			*0.423*	

In the study among those who had IVF and ICSI pregnancy, no significant association was observed between duration of fertility and age distribution. Highest IVF and ICSI pregnancies were observed in the subjectsaged between 30 to 40 years with 5 to 10 years of durationof fertility.

Type of Infertility with respect to age distribution in IVF and ICSI group

Type of Infertility	IVF			ICSI		
	20-30 (n=86)	*30-40 (n=59)*	*>40 (n=4)*	*20-30 (n=56)*	*30-40 (n=51)*	*>40 (n=7)*
Primary Infertility	*56*	*42*	*3*	*40*	*39*	*5*
Secondary Infertility	*30*	*17*	*1*	*16*	*12*	*2*
Total	*86*	*59*	*4*	*56*	*51*	*7*
P value		*0.708*			*0.831*	

In the study among subjects who had IVF pregnancy, there was no significant association between Type of Infertility and Age distribution. Similarly, among subjects who had ICSI pregnancy, there was no significant association between Type of Infertility and Age distribution.

Causes with respect to age distribution in IVF and ICSI group

Causes	IVF Group (149)			ICSI Group (114)		
	20-30 (n=86)	*30-40 (n=59)*	*>40 (n=4)*	*20-30 (n=56)*	*30-40 (n=51)*	*>40 (n=7)*
Anovulation/PCOS	*42*	*20*	*1*	*11*	*7*	*1*
Endometriosis	*10*	*9*	*0*	*6*	*6*	*0*
Tubal Factor	*8*	*9*	*0*	*2*	*1*	*0*
Male Factor	*2*	*6*	*0*	*31*	*28*	*4*
Unexplained	*24*	*15*	*3*	*6*	*9*	*2*
Total	*86*	*59*	*4*	*56*	*51*	*7*
P value		*0.147*			*0.886*	

In the study among those who had IVF pregnancy, there was no significant association between causes and Age distribution. however, a greater number of ICSI cases were done for male factor infertility

Complications in Pregnancy with respect to age distribution in IVF and ICSI group

Complications	IVF				ICSI			
	20-30 (n=86)	30-40 (n=59)	>40 (n=4)	P value	20-30 (n=56)	30-40 (n=51)	>40 (n=7)	P value
Biochemical Pregnancy	**2**	**6**	**1**	**0.04***	**6**	**8**	**4**	**0.006***
Ectopic	1	1	0	0.936	2	1	0	0.789
1st Trimester Abortion	3	4	1	0.144	3	8	2	0.082
Mid Trimester Abortion	0	1	0	0.464	0	0	0	-
Heterotropic Pregnancy	1	0	0	0.691	0	0	0	-
Gestational DM	**4**	**16**	**0**	**<0.001***	2	4	0	0.498
Preeclampsia	6	11	0	0.072	5	6	0	0.593
Pre-Term Labour	**11**	**17**	**0**	**0.032***	5	12	0	0.055
PROM	8	9	0	0.415	4	0	0	0.116
Abruption	2	2	0	0.875	0	0	0	-
Placenta Previa	0	1	0	0.464	0	0	0	-
Multiple Pregnancy	26	10	1	0.191	9	6	0	0.457
IUGR	4	5	0	0.558	0	2	0	0.284
Oligo Hydraminos	**4**	**10**	**0**	**0.036***	6	1	0	0.132
Poly Hydraminos	**0**	**4**	**0**	**0.043***	1	0	0	0.593
P value		0.017*				0.007*		

In IVF group, there was significant difference in Biochemical Pregnancy, Gestational DM, Pre-Term Labour, Oligo Hydraminos and Poly Hydraminos with respect to age distribution. I.e., all the above-mentioned complications were significantly high in mothers in the age group 30 to 40 years compared to other age groups.

There was no significant difference in other complications with respect to age distribution. In ICSI group, therewas significant difference in Bioche mical Pregnancywith respect to age distribut ion.

I.e., Biochemical Pregnancywere significantly high in mothers in the age group 30 to 40 years compared t o other age groups.

There was no significant difference in other complications with respect to age distribution.

Outcome in Pregnancy with respect to age distribution in IVF and ICSI group

Outcome	IVF				ICSI			
	20-30 (n=86)	30-40 (n=59)	>40 (n =4)	P value	20-30 (n=56)	30-40 (n=51)	>40 (n =7)	P value
Preterm Labour	**11**	**17**	**0**	**0.032***	5	12	0	0.055
FTND	19	9	0	0.363	8	5	0	0.474
LSCS Elective	**5**	**21**	**1**	**<0.001***	14	13	1	0.807
LSCS Emergency	20	16	0	0.450	**2**	**18**	**0**	**<0.001***
Vacuum	6	0	0	0.101	2	0	0	0.348
Forceps	1	0	0	0.691	5	12	0	0.055
Total Delivered		126				80		
P value		0.004*				0.041*		

In the IVF group, there was significant difference in Preterm labour, LSCS elective surgery with respect to age distribution. I.e., Preterm labour and Elective LSCS was significantly high in 30 -40 years Mothers compared to other age group.

There was no significant difference in FTND, Emergency LSCS, Vacuum and Forceps delivery. In ICSI group, there was significant difference in Emergency LSCS with respect to age distribution. I.e., Emergency LSCS was significantly high in 30-40 years Mothers compared to other age group.

There was no significant difference in Preterm Labor, FTND, Elective LSCS, Vacuum and Forceps delivery.

Neonatal Outcome with respect to age distribution in IVF and ICSI group

Neonatal Outcome	IVF				ICSI			
	20-30 (n=86)	*30-40 (n=59)*	*>40 (n =4)*	*P value*	*20-30 (n=56)*	*30-40 (n=51)*	*>40 (n =7)*	*P value*
Preterm Birth	***11***	***17***	***0***	***0.032****	*5*	*12*	*0*	*0.055*
LBW	*11*	*9*	*2*	*0.121*	*7*	*5*	*1*	*0.881*
ELBW (<1500g)	*3*	*4*	*0*	*0.591*	*2*	*2*	*0*	*0.869*
MAP	*9*	*6*	*0*	*0.793*	*12*	*14*	*0*	*0.252*
NICU admission	***20***	***29***	***2***	***0.004****	*12*	*14*	*1*	*0.637*
P value		*0.532*				*0.690*		

In the study there was significant difference in Preterm birth and NICU admission in IVF group with respect to age distribution. I.e., Preterm birth and NICU admission were highest in the age group 30 to 40 years mothers respectively.

There was no significant difference in LBW, ELBW and MAP in IVF group with respect to age distribution.

Sex
of New born with respect to age distribution in IVF and ICS I group

Sex	IVF	ICSI
Male	*84*	*54*
Female	*103*	*46*
Total	*187*	*100*

χ 2 =2.152, df =1, p =0.142

In the study there was no significant association between type of pregnancy and gender of new- born. In IVF group, majority of new-
borns was female and in ICSI group majoritywere m ales.

Discussion

The number of pregnancies after ART is still increasing and there is some data showing that IVF/ICSIis associated with a higher rate of complications with regard to both the course of pregnancy and neonatal outcome. Of note, the potential negative impact of micromanipulation techniques should be considered, but only a few research studies have made precise distinctions between IVF and ICSI pregnancies.

Total of 667 patients underwent IVF/ICSI during six-year period between January 2013 to January 2019. Out of these cases pregnancypositive were 263. Of them 63%(149cases) by IVF and 43.3% (114 cases) by ICSI. In the study among subjects in the age group 20 to 30 years, 57.7% had pregnancy by IVF and 49.1% by ICSI. Among subjects in the age group 30 to 40 years, 39.5% had pregnancy by IVF and 44.7% by ICSI. There was no significant association between age and type of pregnancy. In IVF group, there was significant difference in Biochemical Pregnancy, Gestational DM, Pre-Term Labour, Oligo Hydraminos and Poly Hydramnios respect to age distribution.

I.e., all the above-mentioned complications were significantly high in mothers in the age group 30 to 40 years compared to other age groups. There was no significant difference in other complications with respect to age distribution. In ICSI group, there was significant difference in Biochemical Pregnancy with respect to age distribution. I.e., Biochemical Pregnancy were significantly high in mothers in the age group 30 to 40 years compared to other age groups. There was no significant difference in other complications with respect to age distribution. There was increase in incidence of multiple pregnancies with IVF group although it was not statistically significant when compared with age groups.

In a study done by Thompson F et.al [7] compared pregnancies with ART and normal population showed a twofold increased risk of preeclampsia, gestational diabetes, caesarean rates and increased risk of abruption and placenta previa. Study done by Gunby et al [8] rate of multiple pregnancies with IVF is 30% by the Canadian assisted reproductive technologies register.

In the IVF group, there was significant difference in Preterm labour, LSCS elective surgery with respect to age distribution. I.e., Preterm labour and Elective

LSCS was significantly high in 30 -40 years Mothers compared to other age group. There was no significant difference in FTND, Emergency LSCS, Vacuum and Forceps delivery. In ICSI group, there was significant difference in Emergency LSCS with respect to age distribution. I.e., Emergency LSCS was significantly high in 30-40 years Mothers compared to other age group. There was no significant difference in Preterm Labour, FTND, Elective LSCS, Vacuum and Forceps delivery.

According to et.al Fechner et.al study, production of high levels of steroid hormones and other protein peptides resulting from ovarian stimulation increases risk of preterm deliveries. A meta-analysis in literature also showed that singleton pregnancies through IVF/ICSI after single our double embryo transfer are 1.8-2.1 times more prone to risk of preterm deliveries compared with spontaneously conceived pregnancies.[9]

In the study there was significant difference in Preterm birth and NICU admission in IVF group with respect to age distribution. I.e., Preterm birth and NICU admission were highest in the age group 30 to 40 years mothers respectively. There was no significant difference in LBW, ELBW and MAP in IVF group with respect to age distribution. A recent study done by Gibbsons et.al Society for assisted reproductive technology report comparing 60,037 standard IVF cases with 10,176 donor egg and 1,180 gestational carriers found that increased risk of low birth weight, preterm, and extremely low birth babies in IVF cycles [10].

Conclusion

Women who conceived with IVF and ICSI were at higher risk of maternal and perinatal complications particularly with age group 30-40 years. There was significant increase in multiple pregnancies, gestational diabetes and preterm labour and NICU admission in IVF group. Hence with proper diagnosis, stimulation protocol and with single embryo transfer can reduce the risk of multiple birth and further perinatal complications pertaining to advanced age factor.

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