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Neonatal and obstetric outcomes of in vitro fertilization (IVF) and natural conception at a Chinese reproductive unit

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Summary

In vitro fertilization (IVF) has been associated with an increased risk of preterm delivery, caesarean delivery, low and very low birthweight infants. The authors investigated the possible high risks of adverse health outcomes in infants conceived using IVF and intracytoplasmic sperm injection (ICSI). The present study includes 443 infants born to 424 women who conceived naturally and 694 infants born to 536 women that had IVF or ICSI. The study was conducted in the Department of Obstetrics at the Yu Huang Ding Hospital from 2008 to 2009. The main outcome measures were:gestational age, birth weight, mode of delivery, multiple pregnancy rates, and baby gender. The results showed significant differences between the neonatal and obstetric outcomes of IVF/ICSI and natural conception pregnancies. When referred to singletons only, there were no major differences seen in the neonatal and obstetric outcomes between the IVF and the control group.When the IVF group was divided into two sub-groups according to the patient's age (< 35 and ≥ 35 years), there was no statistically significant difference between the two groups in the observed outcomes.

Key words: Neonatal and obstetric outcomes; In vitro fertilization; Multiple pregnancy; eSET.

Introduction

During the past decades, the development of in vitro fertilization (IVF) has resulted in over four million children being born using IVF and the demand for IVF treatment continues to increase. This constant increase is the result of changes in sociodemographic trends such as the decrease in the fertility rates, advanced maternal age, and changes in social trends such as the offer of treatment to single women and same sex couples [1, 2].

Despite the benefits that assisted reproductive technology (ART) offers to a great number of women and couples worldwide, the safety of the procedures has been questioned particularly in their potential to cause health problems in the offspring [3], as compared to the respective rates of adverse health outcomes in naturally conceived children [4].

Some of the adverse outcomes that IVF has been associated with are: an increased risk of preterm delivery, caesarean delivery, and low and very low birth weight [5-7]. Such adverse outcomes may be associated with the increased incidence of multiple pregnancies following IVF [8]. However, it has been shown that singleton IVF pregnancies can also result in preterm delivery and low and very low birth weight infants when compared with spontaneously conceived single pregnancies [9]. IVF twins have similar obstetric and neonatal outcome as compared with spontaneously conceived deliveries [10].

This has been explained, but not conclusively proved, by the increasing age of subfertile women, a factor, which is a well known high risk factor [11]. Advanced maternal age is an important factor and may depend on differences in the studied population characteristics and/or in the obstetric management approach to pregnancies. Nevertheless, even in case control studies the "matching" criteria were not equal, and also the same obstetric unit was present in only three of them [12-14].

The aim of this study, was to compare the obstetric outcomes between IVF and natural conception in different age (≥ 35 and < 35 years) groups of women, providing a particular focus on the differences between singleton and multiple pregnancies.

Materials and Methods

All patients that were pregnant following an IVF cycle were scheduled for delivery between 2008 and 2009 at the Department of Obstetrics at the Yu Huang Ding Hospital.

There was no significant difference between the neonatal and obstetric outcomes for the patients who conceived with intra-cytoplasmic sperm injection (ICSI) or IVF. Patients that underwent oocyte donation, sperm donation, or in vitro maturation, who originally conceived twins, but gave birth to singletons, were excluded from the statistical analysis.

Patients who conceived spontaneously at the same obstetric department during the research period were selected randomly. Age was the only factor considered in the analysis.

The mean (± standard deviation) patient's age at delivery was 31.59 ± 3.48 years in the IVF/ICSI group, and 31.31 ± 3.45 years

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Table 1. — *Comparison of neonatal and obstetric outcome data of 424 spontaneously conceived and 536 conceived after IVF.*

	Control group (n=424)	IVF group (n=536)	*p*
Average age	31.59±3.48	31.31±3.45	0.224
Delivery modes			
Vaginal delivery	225 (53.1%)	70 (13.1%)	< 0.001
Caesarean delivery	199 (46.9%)	466 (86.9%)	
Gestational weeks	38.89±1.92	38.01±1.78	< 0.001
Pre-term labour total	38 (9.0%)	84 (15.7%)	0.002
GA ≤32	5 (1.2%)	3 (0.6%)	0.478
GA ≤34	8 (1.9%)	22 (4.1%)	0.05
GA <37	25 (5.9%)	59 (11%)	0.005
Multiple pregnancy rates	19 (4.5%)	156 (18.2%)	< 0.001
Average birth weight	3,337.97±606.97	3,100.87±642.25	<0.001
VLBW (< 1,500 g)	4 (0.9%)	6 (1.2%)	0.917
LBW (< 2,500 g)	29 (6.5%)	101 (14.6%)	< 0.001
Baby gender			
male	248 (56%)	349 (50.3%)	0.061
female	195 (44%)	345 (49.7%)	

Table 2. — *Comparison of neonatal and obstetric outcome data of 405 spontaneously conceived and 380 conceived after IVF singleton births.*

Singleton	Group (n=405)	IVF group (n=380)	*p*
Average age	31.30±3.45	31.77±3.59	0.062
Delivery modes			
Vaginal delivery	223 (55.1%)	63 (16.6 %)	< 0.001
Caesarean delivery	182 (44.9 %)	317 (83.4%)	
Gestational weeks	39.02±1.76	38.59±1.45	< 0.001
Preterm labour total	30 (7.4%)	20 (5.5%)	0.219
GA < 32	3 (0.7%)	2 (0.5%)	1.000
32 ≤ GA ≤34	7 (1.8%)	5 (1.3%)	0.607
34 < GA <37	20 (4.9%)	13 (3.4%)	0.290
Average birth weight	3,415.51±557.37	3,440.26±510.52	0.518
VLBW (< 1,500 g)	2 (0.5%)	3 (0.8%)	0.943
LBW (< 2,500 g)	14 (3.5%)	9 (2.4%)	0.366

Table 3. — *Comparison of neonatal and obstetric outcome data of 380 singletons and 156 multiple births conceived after IVF*

	Singletons (n=380)	Multiple births (n=156)	*p*
Average age	31.77±3.59	31.13±3.17	0.051
Delivery modes			
Vaginal delivery	63 (16.6 %)	7 (4.5%)	< 0.001
Caesarean delivery	317 (83.4%)	149 (95.5%)	
Gestational weeks	38.59±1.45	36.62±1.78	< 0.001
Preterm labour total	20 (5.5%)	64 (41%)	< 0.001
GA < 32	2 (0.5%)	1 (0.6%)	1.000
GA ≤ 34	5 (1.3%)	17 (10.1%)	< 0.001
GA < 37	13 (3.4%)	46 (29.5%)	< 0.001
Average birth weight	3,440.26±510.52	2,697.01±516.42	< 0.001
VLBW (< 1,500 g)	3 (0.8%)	3 (1.0%)	1.000
LBW (< 2,500 g)	9 (2.4 %)	92 (29.3 %)	< 0.001

in the natural conception group, which was not statistically significant ($p = 0.224$). All women that participated in the study were non-smokers and had no chronic illnesses (i.e. cardiovascular, pulmonary, renal, diabetes or other metabolic diseases).

The main outcome measures for this study were: gestational age, birth weight, mode of delivery, multiple pregnancy rates, and the baby's gender. Gestational age was measured in completed weeks. For the spontaneous conception group, gestational age was based on early fetal ultrasound measures or detailed information on the woman's last menstrual period. For the IVF/ICSI group, gestational age was calculated by adding 14 days to the day of the oocyte retrieval.

Preterm delivery was defined as the birth of the baby whose gestational age was below 37 completed weeks of gestation, and premature delivery was defined as the birth of the baby whose gestational age was below 32 weeks of gestation.

The weight of infants was examined within 24 hours of delivery. Low birth weight (LBW) was defined, as < 2,500 g, and very low birth weight (VLBW) as < 1,500g.

Data analysis was performed using the statistical package SPSS (version 15.0). The means were compared using the independent t-test, the chi-squared test or the Fisher's exact test. Statistical significance was set as $p \leq 0.05$.

This study was approved by the reproductive medicine ethics committee of Weifang People's Hospital. Written Informed Consent Forms were obtained from the patients.

Results

The study included 443 infants born to 424 women after natural conception, which was defined as the control group. The other group studied comprised of 694 infants born to 536 women who had IVF/ICSI, and was defined as the IVF group. In the control group, there were 19 sets of twins, and in the IVF group there were 154 sets of twins and two sets of triplets.

Neonatal and obstetric outcomes are presented in Table 1. As it can be seen, there are some evident differences between the two groups regarding gestational age, birth weight, multiple pregnancy rates, and preterm labour.

The rates of the caesarean sections (CS) were high in both groups, but higher in the IVF group. The difference was statistically significant ($p < 0.001$).

The rate of VLBW and premature delivery was similar in the two groups.

With regards to gender of the baby, the rate of males was 56% in the control group and 50.3% in the IVF group. This difference was not statistically significant, but with reference to the 14 hundred million population of China, it may indicate that the "family's explicit craving" or "sex selection" plays a prominent role in the reason for the increased rate of males in control group.

Table 4. — *Comparison of neonatal and obstetric outcome data of 355 spontaneously conceived and 424 conceived after IVF, defined maternal age < 35 years; 69 spontaneously conceived and 112 conceived after IVF, age ≥ 35 years*

	Age < 35 years			Age ≥ 35 years		
	Control group (n=355)	IVF group (n=424)	*p*	Control group (n=69)	IVF group (n=112)	*p*
Average age	30.13±2.25	30.29±2.49	0.361	37.28±2.19	36.64±1.69	0.042
Delivery modes						
Vaginal delivery	207 (58.3%)	62 (14.6%)	< 0.001	18 (26.1%)	8 (7.1%)	< 0.001
Caesarean delivery	148 (41.7 %)	362 (85.4%)	< 0.001	51 (73.9%)	104 (92.9%)	< 0.001
Gestational weeks	39.04±1.82	38.04±1.79	< 0.001	38.14±2.22	37.89±1.78	0.426
Preterm labour total	26 (7.3%)	68 (16%)	< 0.001	12 (17.4%)	16 (14.3%)	0.575
Multiple pregnancy rate	15 (4.2%)	130 (30.7%)	< 0.001	4 (5.8%)	26 (23.2)	< 0.001
Average birth weight	3,360.35±592.58	3,102.47±629.40	< 0.001	3,224.52±668.09	3,094.57±693.10	0.190
LBW (< 2,500 g)	20 (5.4%)	81 (14.6%)	< 0.001	9 (13%)	20 (14.3%)	0.693

Table 5. — *Comparison of neonatal and obstetric outcome data of 340 spontaneously conceived and 294 conceived after IVF singleton births, defined maternal age < 35 years; 65 spontaneously conceived and 86 conceived after IVF singleton births, age ≥ 35 years.*

Singletons	Age < 35 years			Age ≥ 35 years		
	Control group (n=340)	IVF group (n=294)	*p*	Control group (n=65)	IVF group (n=86)	*p*
Average age	30.14±2.23	30.34±2.49	0.275	37.35±2.22	36.85±1.82	0.138
Delivery modes						
Vaginal delivery	205 (60.3%)	55 (18.7%)	< 0.001	18 (27.7%)	8 (9.3%)	< 0.001
Caesarean delivery	135 (39.7%)	239 (81.3%)	< 0.001	47 (72.3%)	78 (90.7%)	< 0.001
Gestational weeks	39.17±1.62	38.68±1.35	< 0.001	38.25±2.24	38.26±1.69	0.976
Preterm labour total	6 (1.8%)	5 (1.7%)	0.951	4 (6.2%)	2 (2.3%)	0.440
Average birth weight	3437.18±533.14	3455.26±472.54	0.654	3302.15±663.25	3388.95±623.665	0.411
LBW (< 2,500 g)	8 (2.4%)	6 (2.0%)	0.790	6 (9.2%)	3 (3.5%)	0.259

Table 2 represents 405 singletons in the control group and 380 singletons in the IVF group. The mean gestational age was significantly lower ($p < 0.001$) in the IVF group (38.59 ± 1.45 weeks) when compared to the natural conception group (39.02 ± 1.76 weeks).

With regards to the mode of delivery, most women still choose to have caesarean sections. Specifically, 44.9% in the control group and 83.4% in the IVF group had CS a difference which is statistically significant ($p < 0.001$). With regards to the preterm delivery rates (≤ 32, ≤ 34, < 37 weeks) and the average birth weight (VLBW, LBW), there was no significant difference between the two groups.

In Table 3, there is a trend showing that the twins in the IVF group had noticeable adverse neonatal and obstetric outcomes when compared with singletons that were naturally conceived. The rate of premature labour children (GA < 32w VLBW) was similar between the twins and singletons. However, it should be noted that the sample size of this study was not large and could account for this. Further research in this area is necessary to investigate the relationship.

The data in Table 4 describe the neonatal and obstetric outcomes in the two groups (IVF and control) between different age groups (≥ 35 and < 35 years). In the < 35 age group, there were more adverse outcomes in the IVF group compared to the control group. All the data observed were statistically different between the two groups ($p < 0.001$). In the ≥ 35 age group, a statistically significant difference was also presented in the rate of caesarean delivery and multiple pregnancies ($p < 0.001$).

Table 6. — *Comparison of neonatal and obstetric outcome data of 424 aged < 35 years and 112 aged ≥ 35 years conceived after IVF.*

	<35 (n=424)	≥35 (n=112)	*p*
Delivery modes			
Vaginal delivery	62 (14.6%)	8 (7.1%)	0.037
Caesarean delivery	362 (85.4%)	104 (92.9%)	
Gestational weeks	38.04±1.79	37.89±1.78	0.425
Preterm labor total	68 (16%)	16 (14.3%)	0.650
Average birth weight	3,102.47±629.40	3,094.57±693.10	0.897
LBW (< 2,500 g)	81 (14.6%)	20 (14.3%)	0.920
Multiple pregnancy rate	130 (30.7%)	26 (23.2%)	0.123

Table 5 shows the data for the two different age groups (≥ 35 and < 35 years) and refers to singletons only. There were no major differences seen in the neonatal and obstetric outcomes (including the rates of preterm labour and LBW average birth weight) between the IVF and the control group. The IVF group had a statistically significant higher percentage of caesarean deliveries in both age groups (< 35

and ≥ 35 years), when compared to the control group ($p < 0.001$).

The IVF group was divided into two sub-groups according to the patient's age. The first group involved patients with age < 35 years, and the second group involved patients with age ≥ 35 years. The outcomes are presented in Table 6. There was no statistically significant difference between the two groups in all observed outcomes.

Discussion

IVF has been associated with an increased risk of preterm delivery, caesarean delivery, low and very low birth weight infants. In accordance to other studies, these outcomes have also been confirmed in this study. The increased risk of adverse neonatal and obstetric outcome in IVF could be explained primarily by the high incidence of multiple births. However, this may not be the only factor responsible since the literature has shown advanced age of women seeking infertility treatment, to be a well known high risk factor.

Several previous studies have found that singletons conceived with IVF have a poorer outcome compared with singletons who were conceived naturally, when compared with the general population [9, 15, 16]. However, this study does not support these findings, since most of the neonatal and obstetric outcome studied did not differ between the two groups studied (405 singletons in the control group and 380 singletons in the IVF group). This finding indirectly demonstrates that poorer IVF outcome may be associated with the high rate of multiple births. This is confirmed by comparing the 380 singletons and the 115 twins/triplets conceived with IVF, which resulted in a statistically significant difference ($p < 0.001$). This result also demonstrated that the high rates of multiple births in IVF could influence the obstetric outcomes.

Advanced maternal age is another factor that may influence poorer obstetric outcomes after IVF [17-19]. However, this is not supported by all researchers [20]. Since there were no measurable differences found when comparing the two different age groups (< 35 and ≥ 35 years) after IVF, these findings do not support the fact that age may contribute to adverse IVF outcomes.

It is well known that the chance of conceiving decreases with increasing maternal age and that there is a sharp decline in women > 35 years old. Suzuki *et al.*, have shown that obstetric outcomes in pregnancies conceived after IVF may be attributed to mechanisms other than the advanced maternal age though [20].

In other reports, evidence suggests that there is an increased incidence of preterm labour and low birth weight in IVF singletons, when compared to spontaneous pregnancies [7, 16, 19]. However, in this study when comparing 405 singletons from the natural conception group with 380 singletons from the IVF group, there was no significant difference noted. When the results were stratified by age groups (< 35 and ≥ 35 years), there was still no significant difference found.

A possible explanation for this could be the "vanishing twin theory" [21] as these have been eliminated from the crude data. Specifically, from all IVF singletons born, only 10% originated from a twin gestation in early pregnancy. When these singletons were compared with singletons originating from a single gestation, the survivors of the "vanishing twin pregnancy" have been found to be at higher risk of preterm delivery and LBW [21, 22]. Characteristics related to the patients and their individual reproductive/obstetric management might also play a role in these results.

In addition, the high rate of caesarean delivery in the IVF group, which has been observed in many studies before [12, 20, 23] should not be overlooked.The routine use of CS section in IVF patients is performed for many reasons. Firstly, IVF pregnancies are highly valued by the infertile couples and their doctors, and a CS is chosen even for minor complications. Secondly, the IVF population is characterized by advanced maternal age and a large proportion of multiple births post IVF, which can also contribute to the preference for CS. The use of caesareans in such a routine way could cause an iatrogenic increase in caesarean deliveries.

The ultimate goal in ART treatment is the birth of a healthy child. The incidence of multiple pregnancies caused by the replacement of more than one embryo in an attempt to enhance the pregnancy rates, is the most common complication associated with IVF, which may seriously influence the neonatal and obstetric outcomes [24]. Due to these known adversities, many countries initiated the implementation of elective single embryo transfer (eSET) as an effective strategy to minimize the twinning pregnancy rate associated with IVF. The use of eSET and consequent reduction of the twinning rate results in the improved outcome of children born after IVF and has been shown in several recent studies [25, 26].

The Human Embryology and Fertilisation Authority (HFEA), which regulates IVF in the UK, has recently introduced a twin pregnancy target of no more than 15% of all IVF births (www.hfea.gov.uk), and all registered fertility clinics are guided to comply [26]. However, since there is no such regulation in China, eSET is advocated in many reproductive centres, even if improved outcomes are reported in the literature [27, 28].

A major barrier of selecting eSET among clinicians and women is the worry that the use of eSET will reduce overall live birth rates [29, 30]. The fact that eSET may well reduce the chances of having a live birth or resulting in the need for additional treatment cycles makes women, in particular, to refuse eSET. Therefore, a study with a larger sample and adequate statistical power is needed to analyse his matter further and be used for future guidance for the patients.

Even if the incidence of multiple pregnancies is highly related to adverse obstetric outcomes in IVF pregnancies, it is not the sole factor to explain these adversities. Several other factors such as parity, smoking, BMI, alcohol intake during pregnancy, marital status, and years of education are correlated with specific adverse outcomes and may explain the multi-factorial character of such negative outcomes [31].

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