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Comparisons of Perinatal Outcomes among Naturally Conceived and IVF Conceived (Fresh and Frozen Embryos) Singleton Babies

Adhwaa Khudhri[1], Simon Phillips[1,2], Robert Hemmings[3], Wael Jamal[1,4,5] and Mohammad Zubair Alam[6]*

[1]*OVO Fertility Clinic, Canada*

[2]*Department of Obstetrics and Gynecology, University of Montreal, Canada*

[3]*Department of Obstetrics and Gynecology, McGill University, Canada*

[4]*Department of Medicine, University of Montreal, Canada*

[5]*Department of Medicine, Rabigh Campus, King AbdulAziz University, Saudi Arabia*

[6]*King Fahd Medical Research Center, King Abdulaziz University, Saudi Arabia*

Abstract

Infertility is a condition with important psychological, economic, demographic and medical implications. Assisted reproductive technologies started nearly four decades ago can help in alleviating the burden of infertility in affected couples. It is estimated that 1% to 3% of children born in developed countries were conceived through these technologies. The majority of babies born with the help of these assisted reproductive technologies are healthy but, in recent years, health concerns of such babies have come to surface. Studies have found that babies conceived through assisted reproduction have an increased risk of adverse perinatal outcomes. This is a retrospective study on perinatal outcome of singleton babies conceived naturally or using three protocols of assisted reproductive techniques between 2010 and 2014. The perinatal outcome such as gestational age, birth weight and various other parameters of singleton babies conceived through Modified Natural *In Vitro* Fertilization (MNIVF) n=258, *In Vitro* Fertilization using Controlled Ovarian Stimulation (IVFCOS) n=384, and Frozen Embryo Transfer (FET) n=219 were compared to 19,852 naturally-conceived singleton babies. Significant differences (P<0.05) were observed among the spontaneous pregnancy and MNIVF, IVFCOS as well as FET for gestation age, birth weight and sex ratio. Significant differences (P<0.05) were also observed among women in different protocols for anti-mullerian hormone levels, ovarian reserve and type of delivery whereas no significant differences were found for BMI, years of infertility and smoking habits. In conclusion, the differences in perinatal outcomes are still found among babies born after different modes of conceptions. Higher gestation age at delivery was seen in the natural conception group whereas average birth weight was found to be higher in the FET conceived group.

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Correspondence:
Adhwaa Khudhri, OVO Fertility Clinic, 8000 Boulevard Décarie, Montréal, Québec, Canada,
E-mail: dr.akhudari@yahoo.com

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Introduction

Assisted Reproductive Technology (ART) is commonly defined as any procedure that involves handling of eggs, sperm, or both outside the human body (*in vitro*). ART includes *In Vitro* Fertilization (IVF) with or without Intracytoplasmic Sperm Injection (ICSI) and the resulting embryos can be transferred either fresh or after cryopreservation. The ultimate objective of ART is to efficiently achieve healthy live birth outcomes. It has been observed that various processes and procedures associated with ART may increase the risk of adverse outcomes [1,2]. Since the birth of Louise Brown in 1978 until 2008, the world has seen more than 6 million babies conceived through different protocols of IVF [3]. The use of modified natural-cycle IVF which does not involve prior medication to stimulate ovaries has been found to be a reasonable option for women under 35 years of age as it minimizes physical and emotional stress for the patient, significantly reduces the cost of drugs and laboratory tests for the assisted reproduction unit, decreases the chances of multiple pregnancy and ovarian hyper-stimulation, and eliminates the need for the patient to go through a resting cycle [4-6]. While the majority of these IVF babies appeared to be healthy, a higher incidence of some congenital abnormalities, preterm birth and Low Birth Weight (LBW) for gestational age has been noted among ART singletons [7]. The latter problem is of increasing concern since

birth weight is a surrogate for fetal growth and a strong predictor of cardiometabolic disease risk across the life-course [8,9]. Literature also suggests an association between IVF and neurodevelopmental disorders as well as potentially long-term metabolic outcomes [10,11]. Apart from these, it was found that infertility characteristics of the parents may also influence the perinatal outcome [12].

Several other studies have shown ART-aided pregnancies to be associated with a higher risk of complications as compared to spontaneously conceived pregnancies [12-14]. Many previous studies have shown that children born after Frozen Embryo Transfers (FETs) had a higher birth weight and fewer adverse perinatal outcomes as compared to children born after fresh IVF-ICSI [15,16]. Moreover, FET singletons have perinatal outcomes comparable with those observed in naturally conceived singletons [17,18]. The underlying etiologies of these adverse perinatal outcomes are largely unknown but contributing factors may include the sub-fertility of the couple, use of hormonal stimulation, and the use of various ART techniques [12,19]. Moreover, maternal age, smoking, high BMI, and the duration of infertility have also been reported to increase the risk of having a low birth weight [20-22]. Even in the same mother, ART singletons had a poorer outcome as compared to their non-ART-conceived siblings [12]. The present study was done to compare the perinatal outcomes of singleton babies conceived through three different ART protocols and through natural conception to choose the best method of ART for treatment of infertility in a couple.

Material and Methods

This is a retrospective cohort study and included all the patients who had singleton pregnancy and live birth resulting from IVF infertility treatment OVO Clinic which is a university affiliated private fertility center in Montreal, Canada and naturally-conceived singleton babies delivered at St Mary's Hospital which is a community hospital in Montreal, Canada between 2010 and 2014. The scientific-ethical committee at Ovo Clinic Montreal, Canada has approved the study as a quality control analysis. Data for a total of 20,713 births was recorded. The births were distributed according to naturally conceived or by the type of ART protocol used for conceiving by the infertile couples. Thus, the data was organized into four groups: (1) babies conceived naturally without any assistance in normal fertile couples (NAT, n=19852); (2) babies conceived through an ART protocol that involved modified natural IVF (MNIVF, n=258); (3) babies conceived through an ART protocol that involved controlled ovarian stimulation (IVFCOS, n=384); and (4) babies conceived through IVF but only after transfer of frozen embryos (FET, n=219). In the three ART protocols embryos were transferred on day 2, 3 or 5 post-fertilization. The inclusion criteria were maternal age of 41 years and below, gestational age 20 weeks and above, birth weight of 600 grams and above, and BMI of 35 kg/m^3 and below. The exclusions involved women with transfer of more than one embryo, and all multiple births. The data for maternal age, infertility type (primary, secondary), years of infertility, BMI, ovarian reserve, Anti-Mullerian Hormone (AMH) levels, smoking/nonsmoking, insemination type (IVF, ICSI), embryo (fresh, frozen), day of embryo transfer, gestational age, birth weight, sex ratio, and delivery type (caesarian, natural) were collected. Gestational age and birth weight were the primary outcomes and other parameters were the secondary outcomes of the study.

The ART protocol of the MNIVF included monitoring of the cycle at the fertility clinic. The cycle was monitored by ultrasound and Estradiol (E2) measurements. When a single follicle reached ≥ 15 mm and endometrium thickness was ≥ 6 mm, treatment of GnRH antagonist, Orgalotran 250 µg daily (Merck Sharp & Dohme Ltd, The Netherlands) subcutaneously until the trigger day and indomethacin 50 mg orally, three times a day, and HMG 150 IU subcutaneously were given daily (Menopur or Repronex, Ferring Pharmaceuticals Ltd, UK). When the follicle reached >17 mm to 20 mm with and Estradiol and progesterone level are withdrawn the patient received HCG 5000 IU subcutaneously and transvaginal ultrasound oocyte retrieval 34 h to 36 h after HCG administration was performed.

Conventional IVF cycles were performed using standard, long luteal, micro-dose flares, or through GnRH antagonist protocols. Follicular development and estradiol levels were monitored, and the HCG trigger was performed when 3 follicles measuring ≥ 18 mm in diameter were noted. Oocyte retrieval was performed 36 h after HCG trigger. ICSI was performed for male factor or unexplained infertility. For the frozen cycle patients underwent the transfer of their embryos based on different protocols (natural, substituted) for the preparation of the endometrium. The gestational age and birth weight were obtained through a follow-up with the patient or by looking at the delivery records. Pregnancy complications were not part of this study.

Statistical Analysis

Statistical analyses were done by SAS/STAT® software (SAS University Edition, version 9.4M5; SAS Institute Inc. Cary NC, USA). Data were tested for normality by Kolmogorov-Smirnov test and transformed to natural logarithms or ranks as appropriate. NAT, MNIVF, IVFCOS and FET were compared for maternal age, infertility type (primary, secondary), years of infertility, BMI, ovarian reserve, anti-mullerian hormone levels, smoking/nonsmoking, insemination type (IVF, ICSI), embryo (fresh, frozen), day of embryo transfer, gestational age, birth weight, sex ratio, and delivery type (caesarian, natural). One-way analysis of variance was done by using SAS mixed procedure for obtaining a main effect of group. A significant main effect of group was further tested by least significant difference test to locate significant differences among groups. The endpoints with proportions for analysis were compared by chi-square test. A p-value of $p \leq 0.05$ indicated that a difference was significant. Data are presented as the mean ± SEM or as percentages.

Results and Discussion

Throughout the world the use of assisted reproduction treatment has been on the rise though there are still many concerns about the safety of these treatments to both mothers and their neonates. Analysis of published literature have shown that complications and adverse pregnancy outcomes exists for mothers who conceived through assisted reproduction techniques compared with spontaneously conceived pregnancies. These include an increased risk for preterm birth (<37 weeks), low birth weight (<2500 g) and very low birth weight (<1500 g), small gestational age and Caesarean delivery [23,24].

In the present study, we observed a significant difference ($p<0.0001$) between the spontaneous pregnancy and MN-IVF, IVFCOS as well as frozen protocols regarding the maternal age group 30, 38 and 40 years. However, there were no significant differences found for the age at conception among various ART group women. There was a significant difference between the maternal age of patients with spontaneous conception and the maternal age of patients using the three ART protocols. Our results are in accordance

Table 1: Mean ± SD or ratio for various perinatal endpoints for women during various assisted reproduction protocols.

Endpoint		NAT	MNIVF	IVFCOS	FET	P-value
No. of women (n)		19852	238	384	219	
Age (years)		30.69 ± 4.34^{A}	38.78 ± 3.12^{B}	38.63 ± 3.46^{B}	40.39 ± 2.06^{C}	p<0.0001
Gestation age (weeks)		39.13 ± 1.41^{A}	38.37 ± 2.15^{B}	38.11 ± 2.20^{C}	38.57 ± 1.72^{B}	p<0.0001
Birth weight (grams)		3358.2 ± 482.1^{A}	3294.2 ± 38.8^{AB}	3248.0 ±571.4^{B}	3462.9 ± 576.7^{C}	p<0.0001
Sex ratio (male/female)		10231/9619^{AC}	106/130^{B}	209/170^{A}	101/113^{BC}	p<0.05
Delivery (caesarian/natural) hormone (ng/ml)		4921/14931^{A}	70/160^{BC}	103/274^{AC}	72/136^{B}	p<0.0001
Antral Follicular Count		-	17.30 ± 9.90^{A}	21.42 ± 10.46^{B}	22.54 ± 11.64^{B}	p<0.0001
Infertility type primary/secondary		-	154/73	230/136	129/80	p=0.340
Years of infertility 1 year/≥ 2 years		-	134/54	228/81	117/61	p=0.168
BMI	<18.5	-	3	9	8	p = 0.216
(Kg/m^2)	18.6 to 24.9	-	110	118	80	p=0.123
	25.0 to 29.9	-	44	49	42	p=0.598
	>30.0	-	19	40	24	p=0.105
Smoking/non-smoking		-	21/121	29/166	17/104	p=0.978
Insemination type IVF/ICSI		-	112/126^{A}	115/223^{B}	-	p =0.002
Embryo (Fresh/Frozen)		-	-	-	Frozen	-

with a previous investigation on 164 patients who underwent natural modified IVF cycles where live birth rates were significantly lower for women treated for IVF (mean age >36 years) compared with control group whose mean age was 30.7 years [25]. Another study has reported that the ART conceived group were on average 4 years older (36.8 years) compared with the average age of spontaneously conceived group [26]. A large Estonian study has also observed that IVF mothers were older than mothers who conceived spontaneously [27]. We observed that the average gestational age among the spontaneous conception group was 39 weeks whereas it was 38 weeks for MNIVF, IVFCOS and frozen protocols. The difference between spontaneous conception and other methods was found statistically significant with p<0.0001. The birth weight was observed to be higher in the babies born out of frozen protocol followed by the babies born out of natural conception [28]. Compared the BW after fresh (158) and frozen (158) transfer of embryos from the same embryo cohort. Their study shows that BW is significantly higher in the FET than in the fresh embryo transfer group.

On the other hand, no big difference was observed between the birth weights of babies born out of MNIVF and stimulated protocols, IVFCOS. Woo and colleagues have analyzed 494 pregnancies (312 spontaneous and 182 surrogates) and found that the babies born from ART-derived embryos had lower mean gestational age, higher rates of preterm birth, and lower birth weights [29]. A study conducted in Denmark on 3,881 IVF-ICSI mothers and 3,880 spontaneously conceived mothers has observed 65 g lower mean birth weight in assisted reproductive technology children compared with the spontaneously conceived siblings. They further noted a higher risk of low birth weight and preterm birth in IVF/ICSI compared with spontaneous conception [30]. Another investigation compared perinatal outcomes in 174 live singleton births following stimulated IVF *vs.* 190 singleton live births through natural cycle IVF. It reported a higher risk of PTB as well as LBW and an extremely LBW in stimulated IVF group [19]. More male babies than females were born following natural conception and stimulated protocol whereas female babies were predominant in the modified natural and frozen protocols. Other reports from different parts of the world have not found any meaningful difference in sex ratio between spontaneous conception and conception through assisted reproduction techniques [27,31].

Anti-Müllerian Hormone (AMH) is a glycoprotein produced by the ovarian granulosa cells which supports the initial follicular development. It has been widely accepted as a quantitative marker of ovarian reserve [32,33]. It can serve as marker for the prediction of poor response in infertile women [34,35]. Measurement of AMH concentrations in peripheral blood is extensively and successfully used prior to fertility treatments to predict ovarian responsiveness to ovarian stimulation [33,35,36]. The Antral Follicle Count (AFC) on day 2 to 4 of the menstrual cycle is commonly used to determine ovarian reserve. Women with an AFC>15 are identified as having high ovarian reserve [37]. AMH levels have been observed in good correlation with AFC and are relatively stable throughout the menstrual cycle [38,39]. In our study we noted that the AMH was higher in the frozen group compared to the other two groups and ovarian reserve was higher in both IVFCOS and FET groups compared to MNIVF group. Nardo et al. have reported that AMH levels and AFC were markedly raised in the high responders and decreased in the poor responders. Further, prediction of ovarian response through AMH was independent of age. They suggested AMH cut offs of >3.75 ng/mL and <1.0 ng/mL would have modest sensitivity and specificity in predicting the extremes of response and found AMH as a better and superior biomarker than basal FSH and AFC [40]. A study from Netherlands has reported 33 out of 156 women (21.2%) gave live birth. Live birth was significantly lower in women with AMH ≤ 0.1 ng/ml (10.8%) or AMH>0.1 to 0.4 ng/ml (16.7%), compared to 28.6% women with AMH>0.4 to 1.05 ng/ml [35].

Other parameters like type of fertility (primary or secondary), BMI and smoking were not found significant in NMIVF, IVFCOS and frozen groups. Previous reports have also suggested no effect of pre-pregnancy BMI and smoking on adverse obstetrical outcomes between ART and SC pregnancies [41-43]. In conclusion, the present study shows that even keeping maternal factors constant, the

differences in perinatal outcomes can still be found among babies born after different conception methods. The results are consistent with other studies showing a 1 week lower average gestation age at delivery among AT babies compared to naturally conceived pregnancies and a higher average live birth weight in FET singleton babies compared to all other groups. The study suggests that the etiology behind the adverse outcomes in ART conceptions is multi-factorial and is related to both the ART technology and the parental characteristics.

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