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Preterm birth in young women and singleton pregnancy following IVF in the kingdom of Bahrain

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ABSTRACT

Aim: Invitro Fertilization (IVF) rate has been constantly increasing since 1986. Preterm birth is a known complication of IVF pregnancies. Analysis of the risk of preterm birth in young mothers conceived singleton pregnancy through IVF/Intra cytoplasmic sperm injection (ICSI) is an important assessment to counsel young patients contemplating IVF treatment.

Materials and Methods: This is a retrospective analysis of births from young patients of ≤35 years, following natural/ IVF conception between January 2019 and February 2020 at Bahrain Defense Force Hospital. We studied the women who had conceived through ART (Assisted Reproductive Technology) against women conceived naturally. Preterm birth between 24 and 37 weeks of gestation was analyzed. The risk factors for preterm delivery such as multiple pregnancy, placental insufficiency, vaginal infections as well as iatrogenic preterm deliveries were analyzed. P-Value<0.05 is considered statistically significant.

Results: The study included 2646 women. IVF conception was reported in 56 patients with rate of 2.1%. Our study showed that gestational age at delivery was earlier for IVF conception at 36.5 weeks compared to 39 weeks for natural conception. Multiple logistic regression analysis after adjusting other risk factors of preterm delivery, confirmed increased risk of delivery before 37 weeks after IVF singleton conception with OR 2.3 and 95% CI(1.1-4.7) P = 0.02. Risk of delivery before 32 weeks not increased with IVF conception OR 2.3 with 95% CI of 0.9-5.9 P=0.09, but the risk significantly increased for delivery before 28 weeks with OR 4.5 with 95% CI(1.2-16.8)P=0.02.

Conclusion: Preterm deliveries are significantly increased in women aged less than 35 years old after IVF/ICSI with singleton pregnancies.

1. Introduction

Preterm birth is associated with significant neonatal short term morbidities and mortalities as well as long term effects on cardio vascular, respiratory and endocrine system, as well as considerable neurodevelopmental impacts.[1,2] Globally, preterm births are leading to significant economic implications due to the increased death encountered under the age of 5 years as well as organ disabilities in long-term.[3,4] Extreme preterm, birth at gestational age less than 28weeks, even has higher morbidities and mortalities, as perinatal mortality increase as the gestational age decrease.[5,6]

Evidence suggested an increased trend of preterm birth with the rate being 9.8% (8.3–10.9) in 2000 up to 10.6% (9.0–12.0) in 2014. The majority occurred in Asia and sub-Saharan Africa.[7] Reassuringly, another study noted global decrease in the incidence of preterm birth by 5.26%

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between 1990 and 2019. However, the same study showed an increase in preterm birth incidence in the Middle east and north Africa (MENA) from 15.07% to 16.57% over the same period of time.[8] Studies identified many risk factors leading to preterm birth such as multiple pregnancy, maternal age, placentae praevia or iatrogenic factors such as obstetric interventions and IVF.[9–11] IVF increases the risk of preterm birth even in Singleton pregnancy and following embryo reduction.[9,12]

In the last 40years over 8 million babies have been born using IVF treatment.[13] Whilst there is no definitive accurate data available for the Middle East, the estimated IVF market size drawn from a number of cycles by Colliers is roughly 200 million US$ for UAE, 300 million US$ for the Kingdom of Saudi Arabia (KSA) and 500 million US$ for Egypt.[14] There is a steady increase in the population of the MENA region, yet the overall fertility rates have decreased from 7 children per woman in 1960 to less than 3 in 2020. Socio-economic factors such as change in culture, starting family late, increase literacy levels, improve financial independence and the increased use of contraception likely to have contributed to the fertility change. The rise in lifestyle diseases (obesity and diabetes) especially in the Arab countries has also increased the demand for infertility treatments. The accessibility and relax entry requirements add to the increased use of IVF treatment. Furthermore, gender selection as the merely indication for going through IVF treatment with the added embryo screening is widely available without the presence of any fertility issue. Also, the availability of financial coverage by the Government and insurance company in most Arabic countries increases the likelihood of using IVF at early stage of the management.[15] Keeping this increased use of IVF in mind, counselling the couple appropriately before embarking on treatment cycle is very crucial.

Studies identified potential complications during pregnancies post IVF treatment to include increase risk of biochemical pregnancy loss, ectopic, multiple pregnancy, preterm birth, low birth weight, placentae praevia, GDM and cesarean section.[16–18] A prospective follow up study was conducted by Wisborg K et al. on 20,080 liveborn singletons to find the risk of preterm births in pregnant women after fertility treatment. They deduced that unknown characteristics in the couples undergoing IVF-ICSI and the procedure itself had an increased risk of preterm births.[19] Furthermore, a retrospective cohort study by Shi W and group examined the association between preterm delivery and air pollutants in patients undergoing in- vitro fertilization and concluded that air pollutants namely PM2.5, PM10 and N02 exposure during early stages of IVF cycle and pregnancy have an increased risk of preterm delivery in young women.[20]

It is well-known that IVF conception increases preterm delivery in multiple and singletons pregnancies. This study is going to assess the risk of preterm births associated with IVF/ISCI singleton pregnancy in women aged less than 35 years. The risk analysis is done at all types of preterm labor, before 37 weeks, before 32 weeks and before 28 completed gestational weeks. Older patients were not addressed in this study as they were generally treated in accelerated pathways to increase their fertility likelihood and the advance age, solely, can contribute to increase preterm birth.

2. Materials and Methods

The study is a retrospective analysis of young women aged ≤ 35 years, who delivered between January 2018 and January 2019 at Bahrain Defense Force Hospital. The study was approved by the ethical committee research center, Bahrain Defense Force Hospital. Electronic records of women were obtained from fertility unit as well as obstetric unit and the data protection policy rules were followed. Demographic characteristics and data of the mothers collected. All women who attended for delivery at less than 24 gestational weeks were excluded from the analysis. Also, all women aged more than 35 years and who have incomplete notes were excluded as well. Data was anonymized and comparative analysis was performed between IVF/ISCI pregnancies group and naturally conceived group. The main study outcome was the risk of preterm deliveries at three levels: risk of delivery before 37 gestational weeks, risk of delivery before 32 gestational weeks and risk of delivery before 28 gestational weeks.

For patients conceived after IVF treatment, different protocols have been used such as long GnRH agonist, GnRH antagonist and short GnRH agonist. The protocol and gonadotropins were determined according to female age, antral follicular count (AFC), level of follicle stimulating hormone (FSH), previous trials as well as previous responses. Fertility treatments procedures, anticipated risks such as ovarian hyper stimulation syndrome (OHSS), early pregnancy complications, multiple pregnancies and preterm delivery were explained to the couple to their understandable language either in Arabic /English as per fertility unit policy and their consent were obtained before starting the treatment. Embryos were transferred 2–5 days after oocyte retrieval. As the study sample includes all young patients less than 35, the usual practice is to offer single embryo transfer first. Double embryos were transferred according to the IVF unit protocol if there are no medical contraindications, and the patient understands multiple pregnancies risk. Antenatal care for IVF conception is usually hospital-based care.

Demographic characteristics such as age, BMI and parity were calculated. Past Obstetric history such as miscarriages, previous caesarean deliveries and past medical disorders were checked from the case note. Mode of delivery (vaginal/ caesarean delivery), multiple pregnancy

rate, placental abnormalities (previa, abruption), vaginal infection (bacterial vaginosis/ candida), fetal gender, birth weight less than 10^{th} centile were all analyzed between the groups.

2.1. Statistical analysis

Statistical analysis was done using Statdirect software (Version 3.3.5 22/03/2021). The first assessment was done on the data to explore differences between the groups with regards to basic characteristics such as age, BMI, parity, previous obstetric history, and positive medical history. Furthermore, gestational age at delivery, MOD, Placental abnormalities, and vaginal infection were also compared between the groups. Two-sided unpaired t test was used for normally distributed continuous variables, two-sided Mann-Whitney test was used for nonparametric variables and Chi square/ fisher test were used for categorical variables. Then Multiple logistic regression analysis was performed to identify the effect of IVF conception on risk of preterm delivery at different gestational weeks after adjusting for all other contributing risk factors such as age, BMI, parity, any comorbidity, multiple pregnancies, and previous cs. Results presented as OR with 95% CI and P value. P values of less than 0.05 were considered statistically significant.

3. Results

The total number of patients included in this study was 2646. Of this cohort, 56 patients conceived through IVF treatment with rate of 2.1%. The mean age of patients who had IVF conception was 29.2 which was higher than naturally conceived patients with mean age of 27.6. Expectedly, naturally conceiving patients had higher mean parity and previous caesarean rates. There was no difference in BMI, previous medical history, or miscarriage history between the groups (Table 1).

Patients who had IVF conception has higher MP rate at 42% compared to 2.9% in non-IVF conceptions. Furthermore, the IVF group has caesarean rate of 60.7% compared to 20.7% rate for the other group. The median gestational age at delivery was significantly lower in the IVF patients 36.5 gestational weeks compared to 39 weeks for non-IVF patients. Simple comparison between the groups with regards to the rate of singleton preterm rate at different gestational age, noted higher singleton IVF pregnancies delivered between 28-32 weeks, but the difference was not significant for IVF singleton who delivered between 32-37 weeks and before 28 weeks. Interestingly, there were less cases of candida infection in the IVF group 3.6% compared to 14.9% in the natural conception group. This study found no difference in placental abnormalities, bacterial vaginosis cases and birth weight less than 10^{th} centile between the groups (Table 2).

Multiple logistic regression analysis was performed to assess the effect of IVF conception on the risk of delivery before 37 gestational weeks. The analysis adjusted for all other contributing risk factors such as MP, placental abnormalities. Primigravid conception, previous medical history/ caesarean, infection, and age/BMI. The assessment found IVF to increase risk of delivery before 37 weeks with OR 2.3 and 95% CI (1.1-4.7) P=0.02. The analysis also confirmed what is well-known factors associated with preterm delivery such as MP, placenta abnormalities, primigravid conception, and the presence of previous medical history / previous caesarean. Younger patients less than 25 years old has a reduced risk with OR 0.7 and 95% CI (0.6-0.9). Interestingly, BMI and infection did not show any increased risk of delivery before 37 weeks (Table 3).

Multiple logistic regression analysis was also done to assess the risk of IVF on delivery before 32 gestational weeks. The analysis adjusted for all contributing factors as in Table 4. The analysis did not show any increased risk of delivery before 32 weeks with IVF conception OR 2.3 with 95% CI of 0.9-5.9 P=0.09. The analysis showed similar risk factors profile to delivery before 37 weeks except for previous caesarean and maternal age less than 25 (Table 4).

Multiple logistic regression analysis was done to assess the risk of IVF on delivery before 28 gestational weeks. The analysis adjusted for all contributing factors as in Table 5. The analysis showed increased risk of delivery before 28 weeks with IVF conception OR 4.5 with 95% CI of 1.2-16.8 P=0.02. The other risk factors to increase preterm delivery before 28 weeks were placental abnormalities, multiple pregnancies and primigravid conception (Table 5).

4. Discussion

In recent years, the incidence of preterm delivery has increased due to epidemiological and clinical risk factors. IVF conception is associated with preterm delivery in singleton as well as in multiple pregnancy. A study by Li J et al. found that younger women of age less than 25 years had an increased risk of preterm deliveries in IVF even with fetal reduction surgeries.[21] In contrast, our study concluded that younger patients less than 25 years had a reduced risk of preterm deliveries with OR 0.7 and 95% CI (0.6-0.9) after adjusting to the use of IVF for conception or any other confounding factors.

Going through less invasive fertility intervention still produces an increased risk of preterm birth. A large hospital-based cohort study by Messerlian. C et al. assessed preterm births in singleton pregnancies conceived through ovulation induction or stimulation and or intra-uterine insemination. They deduced that preterm births appeared to occur with IUI and donor insemination. Not surprisingly, the high technology assisted reproductive technique group (IVF, ICSI and Gamete Intra Fallopian Transfer) also had a similar correlation.[22] One of the conclusions made by Wu Y et

Table 1: Basic characteristics

	IVF conception N=56 (%)	Natural conception N=2590 (%)	
Mean age in years ± SD	29.2± 3.3	27.6± 4.3	0.001
BMI Kg/M^2 mean ± SD	31.9± 9.6	29.9± 5.8	0.11
Parity mean ± SD	0.7± 0.9	1.8± 1.7	<0.0001
N of previous miscarriages	0.2± 0.5	0.3± 0.6	0.44
H/O miscarriage	11 (19.6)	593 (22.9)	0.57
Previous caesarean	0 (0)	272 (10.5)	0.003
Positive past medical history	7 (12.5)	226 (8.7)	0.32

Table 2: Delivery outcome

	IVF conception N=56 (%)	Natural conception N=2590 (%)	
Gestational age at delivery median (range)	36.5 (26-40)	39 (24-42)	<0.0001
Singleton delivered 32-37 weeks	5/32 (15.6)	207/2515 (8.2)	0.18
Singleton delivered 28-32 weeks	3/32 (9.4)	27/2515 (1.1)	0.006
Singleton delivered<28 weeks	1/32 (3.1)	14/2515 (0.6)	0.17
Caesarean delivery	34 (60.7)	537 (20.7)	<0.0001
Multiple pregnancies	24 (42.9)	75 (2.9)	<0.0001
Birth weight less than 10^{th} centile	4 (7.1)	173 (6.7)	0.79
Placenta abnormalities	4 (7.1)	89 (3.4)	0.13
Bacterial vaginosis	5 (8.9)	284 (10.9)	0.63
Candida infection	2 (3.6)	385 (14.9)	0.01
Fetal gender Male Female	27 (48.2) 29 (51.8)	1334 (51.5) 1256 (48.5)	0.63

Table 3: Risk for delivery <37 gestational weeks

	OR	Coefficient	95% CI	P value
Multiple pregnancies	20.9	3	(12.9-34.3)	<0.0001
Placenta abnormalities	4.8	1.6	(3-7.7)	<0.0001
Primigravid patient	1.5	0.39	(1.1-1.9)	0.007
Presence of positive medical history	1.8	0.6	(1.2-2.7)	0.002
Previous Caesarean birth	1.8	0.6	(1.3-2.6)	0.002
IVF conception	2.3	0.8	(1.1-4.7)	0.02
Age less than 25 years	0.7	-0.3	(0.6-0.9)	0.04
Previous miscarriage	1.2	0.2	(0.9-1.6)	0.16
BMI >30 kg/M^2	1.1	0.07	(0.8-1.4)	0.94
Bacterial vaginosis during pregnancy	0.9	-0.08	(0.6-1.4)	0.56
Candida infection	0.9	-0.08	(0.6-1.4)	0.77

Table 4: Risk of delivery <32 gestational weeks

	OR	Coefficient	95% CI	P value
Multiple pregnancies	10.1	2.3	(4.9-20.6)	<0.0001
Placenta abnormalities	6.4	1.9	(3.1-13.1)	<0.0001
Presence of positive medical history	3.2	1.2	(1.6-6.3)	0.0007
Primigravid patient	2.9	1.1	(1.6-5.1)	0.0002
Previous miscarriage	1.8	0.6	(1-3.3)	0.04
IVF conception	2.3	0.8	(0.9-5.9)	0.09
Previous Caesarean	1.5	0.4	(0.6-3.7)	0.38
Bacterial vaginosis during pregnancy	1.4	0.4	(0.6-3.2)	0.39
Age less than 25 years	1.4	0.3	(0.7-2.4)	0.32
BMI >30 kg/M^2	1.3	0.3	(0.8-2.2)	0.34
Candida infection	0.9	-0.1	(0.4-2)	0.77

Table 5: Risk of delivery <28 gestational weeks

	OR	Coefficient	95% CI	P value
Placenta abnormalities	6.5	1.9	(2.1-19.6)	0.0009
Primigravid patient	4	1.4	(1.5-10.6)	0.004
Multiple pregnancies	7.5	2	(2.3-24.6)	0.001
IVF conception	4.5	1.5	(1.2-16.8)	0.02
Bacterial vaginosis during pregnancy	2.9	1	(0.96-8.9)	0.06
Previous miscarriage	1.5	0.4	(0.6-4.2)	0.41
BMI >30 kg/M^2	1.5	0.4	(0.6-3.7)	0.37
Age less than 25 years	1.3	0.3	(0.5-3.6)	0.61
Previous Caesarean	1	0.01	(0.1-8.1)	0.99
Candida infection	0.3	-1.2	(0.04-2.3)	0.24
Presence of positive medical history	0.5	-0.6	(0.1-4.2)	0.56

al. after a retrospective study comparing the number and quality of frozen thawed embryo transfer in young women was that high quality single blastocyst transfer reduces the risk of preterm delivery.[23] Our analysis was on fresh IVF/ICSI cycles only and revealed that single embryo transfer, which is the protocol for transfer in less than 35 years old patients, is not enough to eliminate preterm delivery after IVF treatment.

A national population- based cohort study assessing the risk of preterm delivery between in vitro fertilization and intra cytoplasmic sperm injection singleton pregnancies was conducted by Morken NH and group. The Norweigian medical birth register data from 1999 through 2006 was used. 5824 singleton pregnancies were identified after IVF and ICSI. The conclusion was that the IVF pregnancies had an increased risk of iatrogenic preterm births between 32 weeks- 36 weeks and 6 days constituting 60% when compared to the ICSI group.[24] Our study, though not looking at the difference between IVF and ICSI, did not identify the increased risk of preterm birth in singleton pregnancies between 32 and 37 weeks. However, when we adjust for all other preterm birth contributing factors, IVF alone increased the risk of preterm singleton delivery with OD of 2.3 95% CI (1.1- 4.7). Comparable findings were reported by Halliday group. They found that preterm births increased two- fold in IVF conceptions when compared to spontaneous conceptions.[25]

A retrospective cohort study by Xiong X et al. obtained data on 97,288 singleton and 40,961 twin conception as a result of fresh non donor IVF cycles. The data obtained was from The Society for Assisted Reproductive Technology Clinic online reporting system from 2006-2010. They deduced that in women less than 30years seeking IVF treatment there is an increased risk of preterm births in singleton pregnancies. The adjusted odds ratio (95%CI) for very early preterm birth (<28 weeks) in women aged 25years – 29 years is 1.3. In the case of early preterm birth (<32 weeks) is 1.2 and preterm birth (<37 completed weeks) is 1.1.[26] Our analysis showed an increased risk of delivery before 28 weeks in young patients with IVF conception OR 4.5 with 95% CI of 1.2- 16.8 which is much higher than the previously reported risk. It is not clear though, if this increased risk is due to ethnic or social differences. Interestingly, our analysis showed no increase in risk of delivery between 28 - 32 weeks in IVF conception with OR 2.3 and 95% CI of 0.9-5.9, p=0.09. This could be due to the size of our sample.

A systematic review of literature was performed by McGovern PG et al to determine whether IVF-ET /GIFT resulting in singleton pregnancies have a risk for preterm births (<37 weeks). Meta-analysis of twenty-seven articles were carried out and it was found that the risk of preterm births was twice than that of natural conception.[27] Our study confirmed that this risk is even higher in patients less than 35 years old. Another systematic review and meta-analysis of cohort studies was carried out by Cavoretto PI et al to assess the risk of iatrogenic preterm deliveries in singleton pregnancies following IVF/ICSI treatment. They concluded that there is an increased risk of iatrogenic preterm births due to abruptio placenta or placenta previa in IVF/ICSI pregnancies.[28] In our study, we found that placental abnormalities were one of the risk factors for preterm delivery prior to 28 weeks.

Severe chorioamnionitis due to candida glabrata in two cases of IVF pregnancies which resulted in preterm delivery and pregnancy loss were reported by Sfameni SF and group. The possible route of entry into the uterus was probably by embryo transfer, through the canula.[29] Surprisingly, in our analysis, there were less cases of Candida in the IVF group (3.6%), in contrast to the non-IVF group (14.9%). Likely patients who had IVF conception with hospital-based care would have been monitored intensely with abrupt treatment to any symptoms. Furthermore, naturally conceived pregnancy tends to have less attendance for screening and potentially patient might consider treating any symptoms of candida without testing and checking with medical team.

A large retrospective cohort study carried out by Lin J and colleagues explored the association of BMI with preterm birth and low birth weight in 18,683 singleton

infants born after frozen- thawed transfer of embryos. The study found overweight patients were significantly associated with preterm birth (adjusted OR 1.52 95% CI-1.30-1.77) and consistent in all age categories.[30] From our study we deduced that BMI had no co-relation with preterm delivery in singletons who were the result of IVF conception in young women less than 35 years.

5. Limitation and Strength of Study

Analysing young age group specifically, focus the needed counselling for patients who might embark on treatment before exploring other fertility options. However, the duration of infertility before IVF was not analysed which could influence the decision to proceed with IVF. As with shorter periods of infertility, a less invasive mode of treatment could be offered if visible. The indication analysis will help as well to clarify any IVF done as patient preference/choice; action due to the social pressure associated with infertility in the Middle East. Further research is needed to address subgroup analysis of frozen/fresh embryo transfer and IVF /ICSI procedures which could assess any increased risk of preterm delivery in such groups.

6. Conclusion

IVF /ICSI treatment increases preterm delivery in patients less than 35 years old with singleton pregnancy. The risk of extreme preterm birth and associated mortalities and morbidities raised the importance of counselling in younger women before embarking on IVF treatment. In younger patients all other less invasive fertility treatment options should be considered and discussed meticulously. The increased odds of extreme preterm birth in IVF/ICSI younger women with singleton pregnancies, call attention for further studies to assess the current practice in the fertility treatment to identify any modifiable risk factors to improve the practice.

7. Availability of Data and Materials

The data supporting the study are included in the article and the data analysed during the current study available from the corresponding author on reasonable request.

8. Ethical Declaration

The study was performed according to the standard of our Institute, Bahrain Defense Force Hospital. The study was conducted after the approval of the ethical committee, the Crown Prince Centre for Training and Medical Research, Ref: BDF/R&REC/2022-472.

9. Consent for Publication

Not Applicable.

10. Sources of Funding

None.

11. Conflict of Interest

None.

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