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ORIGINAL ARTICLE

Congenital Anomalies in Neonates Conceived by in Vitro Fertilization; Hospital-Based Study

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Abstract

Background: *The percentage of children born after in vitro fertilization will continue to increase due to demographic changes such as increasing maternal age and new developments in assisted reproduction techniques. In vitro fertilization conceptions may carry an increased risk of congenital malformations.*
Objective: *To measure the rate of congenital anomaly for neonates born by In vitro fertilization in comparison to the rate of congenital anomalies in neonates born by natural conception in Baghdad Teaching Hospital.*
Patients and methods: *This study is a case control study conducted in Neonatal Intensive Care Unit of Baghdad Teaching Hospital in medical city through the period from 1st of May to 30th of November, 2018 on in vitro fertilization births. The congenital anomaly rate in the general population was derived from routine register of congenital anomalies in department of statistics of Baghdad teaching hospital ,where as the rates within in vitro fertilization population are derived from detailed examination and follow up.*
Results: *The rate of congenital anomaly among neonates born spontaneously in Baghdad Teaching Hospital was 1.2%, while rate of congenital anomaly among neonates born by in vitro fertilization in Baghdad Teaching Hospital was 26% comonly central nervous system where five cases detected. There was a high significant association between multiple pregnancies and in vitro fertilization neonate and a high significant association between positive consanguinity and in vitro fertilization neonates with anomalies.*
Conclusions: *The rate of congenital anomalies for infants born by in vitro fertilization is higher than rate of congenital anomalies for infants born by spontaneous birth in Baghdad Teaching hospital.*

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Keywords: In vitro fertilization, Congenital anomaly, Consanguinity.

1. INTRODUCTION

In vitro fertilization (IVF) was first developed as a method to overcome bilateral Fallopian tube obstruction. The procedure includes several steps: (1) the woman's egg is retrieved from the ovaries; (2) exposed to sperm outside the body and fertilized; (3) the embryo(s) is cultured for 3 to 5 days; and (4) is transferred back to the uterus. IFV is considered to be one of the most effective treatments for infertility today. According to data from the Canadian Assisted Reproductive Technology Registry, the average live birth rate after IVF in Canada is around 30%, but there is considerable variation in the age of the mother and primary cause of infertility. An important advantage of IVF is that it allows for the control of the number of embryos transferred. An elective single embryo transfer in IVF cycles adopted in many European countries was shown to significantly reduce the risk of multiple pregnancies while maintaining acceptable birth rates. However, when number of embryos transferred is not limited, the rate of IVF-associated multiple pregnancies is similar to that of other treatments involving ovarian stimulation (1). The rate of birth defects following In Vitro Fertilization Embryo Transfer (IVF) varies from 3.4 to 9.0% (2). The comparison of intracytoplasmic sperm injection and IVF children taking part in an identical follow-up study did not show any increased risk of major malformations in the intracytoplasmic sperm injection group (3). Control selection (national or clinical control) from a different population creates the problem of differences in screening methods (4), management of pregnancy, and perinatal care between cases and controls (2). In both cases, only stratification procedures reveal the influence of assisted reproductive technology on the incidence of birth defects. However, the results between studies were inconsistent (5, 6). Congenital birth defects and early/premature births are common and complex conditions related to perinatal/infant mortality and morbidity throughout the world. Particularly, babies born from infertile couples after ART treatments represents a major clinical and epidemiological issue, especially considering that 1 to 2 % of babies born annually are conceived after ART procedures. The evaluation of risk for congenital defects and/or premature delivery is a fundamental step for an adequate pre-conception counseling. Recent advances in fetal/neonatal care have improved clinical outcomes for these babies; however, major congenital defects and the

associated disabilities have a big impact on children and families' lives with social and ethical implications (7).

Neonatal Outcomes in IVF-conceived offspring:

Numerous studies conducted in China and other countries have explored the type and incidence of ART-related side effects in offspring. Although most studies of ART offspring to date have demonstrated no added risk for developmental problems, potential difficulties for children born after ART include issues such as multiple gestation and prematurity and elevated risks of birth defects and genetic disorders 1-3.

1. Multiple gestation and prematurity
2. Low birth weight and intrauterine growth restriction (IUGR) in IVF-conceived singletons
3. Congenital malformations and genetic disorders

2. METHODOLOGY

This study is a case control study conducted in Neonatal Intensive Care Unit (NICU) of Baghdad Teaching Hospital in medical city through the period from 1st of May to 30th of November, 2018. All IVF births, delivered in obstetrical department of Baghdad teaching hospital were included in this study, examined for apparent congenital anomalies. Those IVF births having apparent congenital anomalies were compared with different variables (gender, birth weight, Parity, maternal age, paternal age, types of anomalies, consanguinity, and outcome.) with neonates born by natural conception having apparent congenital anomalies. All neonates born in NICU of Baghdad teaching hospital were examined by neonatologist, pediatricians, resident doctor for major and minor congenital anomalies, confirmation of internal defects was done by various confirming studies like X-Ray, ultrasound, and echocardiography if there was any suspicion. The congenital anomaly rate in the general population (neonate delivered by natural conception) was derived from routine register of congenital anomalies in department of statistics of Baghdad teaching hospital ,Where as the rates within IVF population are derived from detailed examination and follow up. Information about the pregnancy regarding IVF techniques were taken from the mothers, IVF cards as it was done in private fertility IVF center.

Follow up:

Follow up after birth was limited to early neonatal period and it was incomplete.

Data Collection:

The data was collected from the parents and neonatal records saved in fertilization cards for IVF neonates, filled in a prepared questionnaire. The questionnaire included the followings.

1. Gestational age and gender of neonates.
2. Neonatal birth weight.
3. Mode of delivery.
4. Type of parity: Single or multiple.
5. Congenital anomaly.
6. Outcome: Alive or dead.
7. Parental age.
8. Maternal risk factors: DM, HT and drugs history.
9. Consanguinity.

Ethical considerations:

1. The ethical approval was taken from Arab Board for Health Specialties and hospital authorities.
2. Administrative agreement was taken from Baghdad Teaching Hospital administration.
3. Confidentiality was taken in consideration.

Statistical analysis:

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 20 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi square test used for categorical variables and Fishers exact test was used when total of expected variables was less than 205. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs. Statistical analysis of the study was done by Specialist in Community Medicine.

3. RESULTS

This study included 50 IVF neonates with mean gestational age of 31.9±3 weeks; 44% of them were born in gestational age of less than 32 weeks, 50% of them born in age group 32-37 weeks and 6% of them were born in age group ≥37 weeks. IVF neonate males were more than females with male to female ratio as 1.17:1. Mean birth weight of IVF neonates was 1.9±0.8 Kg; 44% of neonates had birth weight less than 1.5 Kg, 36% of them had birth weight of 1.5-2.4 Kg and 20% of them had birth weight of 2.5 Kg and more. The majority 94%of IVF neonates were delivered by cesarean section while only 6% of them were delivered by normal vaginal delivery. Single pregnancy constituted 24% (12 baby) of IVF neonates, eight twin pregnancy 32% (16 baby), six triplet pregnancy 36 % (18 baby) and one quadruplet pregnancy 8% (4 baby). All these findings were shown in (**Table 1**). The congenital anomalies was present among(26%)of IVF neonates; the congenital anomaly types were hydrocephalus (23.1%), Down syndrome (15.4%), transposition of great arteries (7.7%), diaphragmatic hernia (7.7%), dextrocardia (7.7%), sacrococcygeal teratoma (7.7%), tracheoesophageal fistula (7.7%), meningomyelocele (7.7%), esophageal atresia (7.7%) and anencephaly (7.7%). Alive outcome was shown for (80%) of IVF neonates while dead neonates (20%) of them. Mean IVF neonatal fathers age was 37.9±3 years; 76% of them were less than 40 years age. Mean IVF neonatal mothers age was 31.2±3.6 years; 54% of them were 35 years age and more. Diabetes mellitus was present among 6% of IVF neonate mothers and HT was present among8% of IVF neonate mother. Positive drug history was shown in 10% of IVF neonate mothers and positive consanguinity was detected in 82% of IVF neonate mothers. All these findings were shown in (**Table 2**). The incidence of congenital anomaly among neonates born spontaneousely in Baghdad Teaching Hospital was 1.2%, while incidence of congenital anomaly among neonates born by IVF in Baghdad Teaching Hospital was 26%. All these findings were shown in (**Table 3**). No significant differences between IVF and spontaneous anomaly neonates regarding gender ($p=0.8$). There was a significant association between IVF neonates and lower birth weight ($p=0.01$). All these findings were shown in (**Table 4**). There was a highly significant association between multiple pregnancies and IVF neonates ($p<0.001$). A highly significant association was observed between high congenital anomaly incidence and IVF neonates ($p<0.001$; OR=29.6). No significant differences between IVF and

spontaneous anomaly neonates regarding types of congenital anomalies (p=0.1). All these findings were shown in (**Table 5**). No significant differences between IVF and control neonates regarding father age (p=0.8) and mother age (p=0.2). There was a highly significant association between positive consanguinity and IVF neonates (p<0.001; OR=20.9). All these findings were shown in (**Table 6**). There were no significant differences between IVF and spontaneous anomaly neonates regarding outcome (p=0.7) this finding shown in (**Table 7**).

Table 1: Gestational age and general characteristics of IVF neonates.

Variable		No.	%
Gestational age mean±SD (31.9±3 weeks)	<32 weeks	22	44.0
	32-37 weeks	25	50.0
	≥37 weeks	3	6.0
Neonatal gender	Male	27	54.0
	Female	23	46.0
Birth weight mean±SD (1.9±0.8 Kg)	<1.5 Kg	22	44.0
	1.5-2.4 Kg	18	36.0
	≥2.5 Kg	10	20.0
Mode of Delivery	Normal vaginal delivery	3	6.0
	Cesarean section	47	94.0
Delivery (Parity)	Single	12	24.0
	multiple	38	76.0
	Total	50	100.0

Table 2: Congenital anomalies, characteristic and outcome of IVF neonates.

Variable		No.	%
Congenital anomaly	Yes	13	26.0
	No	37	74.0
	Total	50	100.0
Congenital anomaly types	Transposition of great arteries	1	7.7
	Hydrocephalus	3	23.1
	Down Syndrom	2	15.4
	Diaphragmatic hernia	1	7.7
	Meningomyelocele	1	7.7
	Esophageal atresia	1	7.7
	Dextrocardia	1	7.7
	Sacrococcygeal teratoma	1	7.7
	Anencephaly	1	7.7
	Tracheoesophageal fistula	1	7.7
	Total	13	100.0
Neonatal outcome	Alive	40	80.0
	Death	10	20.0
Father age mean±SD (37.9±3 years)	<40 years	38	76.0
	≥40 years	12	24.0
Mother age mean±SD (31.2±3.6 years)	<35 years	23	46.0
	≥35 years	27	54.0
DM	Yes	3	6.0
	No	47	94.0
HT	Yes	8	16.0
	No	42	84.0
Drug history	Positive	5	10.0
	Negative	45	90.0
Consanguinity	Positive	41	82.0
	Negative	9	18.0
	Total	50	100.0

Table 3: Rate of congenital anomaly.

Type	Total birth (No.)	Anomalies (No.)	Incidence/year (%)
Spontaneous Conception	4100	48	1.2
IVF	50	13	26

Table 4: Distribution of gender and weight according to IVF and spontaneous anomaly neonates.

Variable		IVF		Natural conception		P-Value
		No.	%	No.	%	
Neonatal gender	Male	7	53.8	25	52.1	0.8*^{NS}
	Female	6	46.2	23	47.9	
Neonatal birth weight	<1.5 Kg	4	30.8	3	6.3	0.04*^{S}
	1.5-2.4 Kg	5	38.5	29	60.4	
	≥2.5 Kg	4	30.8	16	33.3	

**Chi-square test, NS=Not significant, S=Significant*.

Table 5: Distribution of general characteristics and anomalies according to IVF, spontaneous anomaly neonates.

Variable		IVF		Natural ception		P-Value
		No.	%	No.	%	
Delivery (Parity)	Single	7	53.9	47	97.9	<0.001*^{S}
	multiple	6	46.1	1	2.1	
Congenital anomaly	Yes	13	26	48	1.2	<0.001*^{S} OR=29.6 CI{14.8-59.3}
	No	37	74	4052	98.8	
Congenital anomalies	Cardiovascu	2	15.4	11	22.9	0.1**^{NS}
	Neurologica	5	38.4	13	27.1	
	Gastrointes	2	15.4	2	4.2	
	Chromoso	2	15.4	3	6.3	
	Respiratory	1	7.7	1	2.1	
	Musculoske	0	-	3	6.3	
	Sacrococcy	1	7.7	0	-	
	Others	0	-	15	31.2	

**Chi-square test, NS=Not significant, S=Significant*.

Table 6: Distribution of father and mother risk factors according to IVF and spontaneous anomaly neonates.

Variable		IVF		Natural conception		P-Value
		No.	%	No.	%	
Father age	<40 years	7	53.8	30	62.5	0.8^{NS}
	≥40 years	6	46.2	18	37.5	
Mother age	<35 years	3	23.1	22	45.8	0.2^{NS}
	≥35 years	10	76.9	26	54.2	
Consanguinity	Positive	11	84.6	10	20.8	$<0.001^{S}$ OR=20.9 CI{3.9-109.9}
	Negative	2	15.4	38	79.2	

**Chi-square test, NS=Not significant, S=Significant*.

Table 7: Distribution of outcome according to IVF and

Outcome					P-Value
Alive	7	53.8	21	43.7	0.7^{NS}
Death	6	46.2	27	56.3	
total	13		48		

4. DISCUSSION

The assisted reproductive technologies have been widely increased in last decades to reach 1% of births in USA and 4.3% of births in Europe (8). However, after long period application of these technologies, multiple adverse effects had been shown like congenital anomalies, premature birth, low birth weight and small for gestational age in comparison to spontaneous birth (9). Congenital malformations were observed in this study 13/50 IVF children (26%) and 48/4100 of the control children (1.2%) who born by natural conception (odd ratio 29.6). This significant difference in percentage could be due to that pregnant IVF mother are referred to medical city (tertiary center) for delivery because of high risk factors such as multiple pregnancy, preterm labor or diagnosed intrauterine with congenital anomalies. Those mothers who don't have risk factors delivered in other public and private

Hospitals where the procedure of IVF was done that's why the sample is small. Present study showed that rate of congenital anomalies in IVF births in Baghdad Teaching Hospital was 26% this rate higher than the result in Netherlands(3.6%), natural conception (2.7%) by Anthony (10), Olson et al. IVF(6.2%) natural conception(4.4%) (11). Another previous study carried out by Hansen et al. (12) in UK revealed that conception by IVF is associated with double risk of congenital anomaly development were highly related to IVF conception than natural conception (IVF9%), natural conception (4.2%).The rate of current study is close to results of Ooki study in Japan (13) which reported an incidence rate of 10-30% for congenital anomalies in neonates born by ART. Khalaf study in Iraq (14) reported that 10% of neonates born after assisted reproductive techniques in 3 hospitals in Baghdad had congenital malformations.

Inconsistent with our findings, Han et al. (15) retrospective cohort study in China evaluated the congenital anomaly incidence in infants born by ART and in spontaneous birth and found no significant difference in incidence between two groups; also they reported no significant difference in congenital anomaly incidence between in vitro fertilization and intracytoplasmic sperm injection. These inconsistencies may be related to different reasons such as different advancement in ART technology between different centers, discrepancy in consanguinity prevalence between societies and differences in study designs and sample sizes. Although no significant differences in types of anomalies between congenital anomalies of IVF and those of spontaneous birth in present study, Källén et al. (16) study in Sweden showed that infants born with IVF had more cardiovascular malformations and limb defects than spontaneous birth neonate. Another previous study carried out by Hansen et al. (12) in UK revealed that conception by IVF or ICS is associated with double risk of congenital anomaly development and the anomalies of musculoskeletal and urogenital systems were highly related to IVF conception than normal infants. Several studies have investigated the incidence of congenital malformations in IVF conceptions; some report a possible increase in the incidence of central nervous system (CNS) defects, as in this study where 5cases of CNS defect were observed (10). This study showed also a highly significant association between multiple pregnancies and IVF neonates ($p<0.001$). This finding coincides with results of Zheng et al. (17) study in China which found that risk of congenital anomaly for multiple

pregnancy achieved by IVF is significantly increased than pregnancy by spontaneous birth. Many authors such as Hu et al. (18) in South Korea, Liberman et al. (19) in USA and Qin et al. (20) in China in their studies had been shown that multiple pregnancy occurred by conception with IVF is accompanied by higher risk of congenital anomalies as compared to infants born by spontaneous birth. Despite these findings; specific determination of congenital anomaly types that are associated with multiple pregnancy of IVF conception is unknown. One of the most important individual effects on children's health following increased ART treatments is the chance of multiple pregnancies occurring following transferring more than one embryo. Total risk of multiple pregnancies demonstrably increases in women using ART. Notably, most of these pregnancies are dizygotic and as far as the adverse outcomes of monozygotic pregnancies are higher, this indicates the decreased possibility of congenital malformations in multiple pregnancies following ART, compared to SC Hoorsan et al. (21). Multivariate analysis was performed to determine independent predictors of congenital anomalies (CAs) in the IVF such as maternal age. In the IVF, CAs were not significantly correlated to maternal age as in our study, the anomalies increased with age>35years but statistically insignificant Han et al. (15). There are different study assessed sperm quality declining on relation to paternal age and its impact on in vitro fertilization (IVF) outcomes in order to estimate the APA (Advanced Paternal Age) cut off. IVF outcomes also were affected by paternal age as indicated by the rates of cancelled embryo transfers, clinical pregnancy and miscarriage in the two groups APA and Y (29%, 17%, and 60% vs. 10%, 32%, and 42%). Finally, statistical analysis of the results suggests that the age of 40 should be considered as the APA cutoff during ART attempts. Current guidelines on genetic risk assessment and counseling for advanced paternal age are general and provide no clear definition of what age constitutes advanced paternal age . No screening or diagnostic test panels specifically target conditions associated with advanced paternal age. In summary, indicates that paternal age is associated with certain birth defects, and this association could provide clues to the etiology of these conditions. Ultimately this might lead to consideration of paternal as well as maternal age in counseling couples about risk for affected offspring(16). Current study showed a highly significant association between positive consanguinity and IVF neonates ($p<0.001$; OR=20.9). Consistently, Chen et al. (22) study in

Taiwan reported higher consanguinity prevalence among infertile couple fertilized with IVF and ended in high incidence of hydrocephalus. Kurinczuk et al stated that risk of death and congenital anomalies was increased three times among infants born by IVF with parents having positive consanguinity (23). In this study, there was no significant difference between IVF and spontaneous anomaly neonates regarding outcome. These findings are similar to results of Davies et al. (24) study in Australia which found that birth defects were higher among newborns of IVF , but the morbid outcomes and death rates for infants born by IVF was not significantly different from normal population. However, Koivurova et al. (25) study in Finland found that neonatal outcomes after IVF are worse than general population. These differences are due to variance factors related to fertilization centers and variant sample size.

Limitations of the study:

1. Single center study.
2. Short period study.
3. Loss to follow up.
4. IVF neonate who referred from private hospital and delivered in Baghdad teaching hospital either for preterm complication or congenital anomalies.

5. CONCLUSIONS

The rate of congenital anomalies for infants born by in vitro fertilization is higher than rate of congenital anomalies for infants born by spontaneous birth in Baghdad Teaching hospital.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients enrollment were in accordance with Declaration of Helsinki of World Medical Association , 2013 for the ethical principles of researches involving human. Signed informed consent was obtained from each participant and data were kept confidentially.

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