

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

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Original Article

Summary

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% commonly 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.

Keywords: In vitro fertilization, Congenital anomaly, Consanguinity

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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. IVF 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. PATIENTS and METHODS

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 following data; gestational age and gender of neonates, neonatal birth weight., mode of delivery, parity (single or multiple), congenital anomaly, outcome: alive or dead, parental age, maternal risk factors such as DM, HT , drugs history and consanguinity.

Statistical analysis

Patients' data were entered, processed and analyzed using the statistical package for social sciences (SPSS) version 20. Descriptive statistics presented as (mean \pm standard deviation) for scale variables and frequencies and percentages for categorical variables. Appropriate statistical tests were performed according to the type of variables at a level of significance , two tailed (p value) of ≤ 0.05 to be significant. Statistical analysis was performed with the aid of Specialist in Community Medicine and biostatistics.

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% at 32-37 weeks and 6% were born in age group ≥ 37 weeks. IVF neonate males were relatively dominant in a male to female ratio of 1.17:1. The mean birth weight of IVF neonates was 1.9 ± 0.8 Kg; 44% of neonates had birth weight less than 1.5 Kg, 36% had birth weight of 1.5-2.4 Kg and 20% had birth weight of 2.5 Kg and more. The majority, 94%, of IVF neonates were delivered by cesarean section while only 6% delivered by normal vaginal delivery. Single pregnancy constituted 24% (12 baby) of IVF neonates, while multiple gestations reported in 38 (76%) of IVF pregnancies where eight twin pregnancy 32% (16 baby), six triplet pregnancy 36 % (18 baby) and one quadruplet pregnancy 8% (4 baby), (Table 1). Congenital anomalies were reported in 13 (26%) IVF neonates; these included 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%) , (Table 2). Among IVF neonates , 40 (80%) were survived, while 10 (20%) unfortunately died , (Figure 1). The mean age of IVF neonates' fathers was 37.9 ± 3 years; 76% of them were younger than 40 years. For IVF

neonates' mothers the mean age was 31.2 ± 3.6 years; 54% of them aged 35 years or older. Among the neonates' mothers, history of diabetes mellitus (DM) reported in 6% , hypertension in 16% and history of medication use reported in 10% of IVF neonates' mothers. Positive drug history was shown in 10% of IVF neonate mothers. Positive consanguinity was detected in 82% of IVF neonate mothers, (Table 3). The incidence of congenital anomaly among neonates delivered from spontaneous conception in was 1.2%, while incidence of congenital anomaly among neonates of IVF group was 26%, (Table 4). No significant differences between IVF and spontaneous conception groups regarding gender of neonates ($P > 0.05$). A significant association between IVF conception and lower birth weight ($P < 0.05$), (Table 5). With a highly significant difference, congenital anomalies were more frequent in IVF than spontaneous conception group; 26% vs. 1.2%, respectively, with an odds ratio (OR) of 29.6, indicated that women conceived by IVF were about 30-fold more likely to have neonates with congenital anomalies, (Table 6). Multiple gestations were significantly associated with congenital anomalies in IVF group compared to spontaneous conception group; 46.1% vs. 2.1%, respectively, ($P < 0.001$). No significant differences were found in fathers' age and mothers' age, between IVF and spontaneous conception groups with anomaly neonates. There was a highly significant association between positive consanguinity and IVF anomaly neonates ($p < 0.001$; $OR = 20.9$), (Table 7). No significant differences between IVF and spontaneous conception anomaly neonates regarding outcome ($P > 0.05$), (Table 8).

Table 1. Gestational age and general characteristics of IVF neonates (N=50).

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

Table 2. Distribution of congenital anomalies among IVF neonates (N=50).

| Congenital anomaly | No. | % |
|-----------------------------------|-----|------|
| None | 37 | 74.0 |
| Yes | 13 | 26.0 |
| Types of Congenital anomalies | | |
| • Hydrocephalus | 3 | 23.1 |
| • Down Syndrom | 2 | 15.4 |
| • Transposition of great arteries | 1 | 7.7 |
| • 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 |

Table 3. Characteristic of IVF Neonates' parents (N=50)

| Variable | No. | % | |
|--------------------------------------|-----------------------------|------|------|
| Father age | <40 years | 38 | 76.0 |
| | ≥40 years | 12 | 24.0 |
| | Mean (SD): 37.9 (3.0) years | | |
| Mother age | <35 years | 23 | 46.0 |
| | ≥35 years | 27 | 54.0 |
| | Mean (SD): 31.2 (3.6) years | | |
| Medical history of neonates' mothers | Diabetes mellitus | 3 | 6.0 |
| | Hypertension | 8 | 16.0 |
| | Medication use | 5 | 10.0 |
| Positive consanguinity | 41 | 82.0 | |

Table 4. Incidence rate of congenital anomaly.

| Type | Total birth | Anomalies | Incidence/year (%) |
|------------------------|-------------|-----------|--------------------|
| Spontaneous Conception | 4100 | 48 | 1.2 |
| IVF | 50 | 13 | 26.0 |

Table 5. Distribution of gender and birth weight of neonates with congenital anomalies in IVF and spontaneous conception groups

| Variable | | IVF | | Spontaneous conception | | P |
|--------------|------------|-----|------|------------------------|------|-------|
| | | No. | % | No. | % | |
| Gender | Male | 7 | 53.8 | 25 | 52.1 | 0.800 |
| | Female | 6 | 46.2 | 23 | 47.9 | |
| Birth weight | <1.5 Kg | 4 | 30.8 | 3 | 6.3 | 0.040 |
| | 1.5-2.4 Kg | 5 | 38.5 | 29 | 60.4 | |
| | ≥2.5 Kg | 4 | 30.8 | 16 | 33.3 | |

Table 6. Frequency distribution of congenital anomalies according to IVF and spontaneous conception

| Congenital anomaly | IVF group | | Spontaneous conception group | |
|--------------------------------------|-----------|----|------------------------------|------|
| | No. | % | No. | % |
| Yes | 13 | 26 | 48 | 1.2 |
| No | 37 | 74 | 4052 | 98.8 |
| OR=29.6 , 95%CI [14.8-59.3], P<0.001 | | | | |

Table 7. Distribution of risk factors of congenital anomalies according to IVF and spontaneous conception

| Variable | | IVF group | | Spontaneous conception group | | P |
|-------------------|-----------|-----------|------|------------------------------|------|---|
| | | No. | % | No. | % | |
| Type of Gestation | Single | 7 | 53.9 | 47 | 97.9 | <0.001 |
| | Multiple | 6 | 46.1 | 1 | 2.1 | |
| Father age | <40 years | 7 | 53.8 | 30 | 62.5 | 0.800 |
| | ≥40 years | 6 | 46.2 | 18 | 37.5 | |
| Mother age | <35 years | 3 | 23.1 | 22 | 45.8 | 0.200 |
| | ≥35 years | 10 | 76.9 | 26 | 54.2 | |
| Consanguinity | Positive | 11 | 84.6 | 10 | 20.8 | OR=20.9 95%CI [3.9-109.9] P<0.001 |
| | Negative | 2 | 15.4 | 38 | 79.2 | |

Table 8. Outcome of congenital anomalies neonates in IVF and spontaneous conception groups.

| Outcome | IVF group | | Spontaneous conception group | |
|---------------------------------|-----------|-------|------------------------------|-------|
| | No. | % | No. | % |
| Alive | 7 | 53.8 | 21 | 43.7 |
| Death | 6 | 46.2 | 27 | 56.3 |
| Total | 13 | 100.0 | 48 | 100.0 |
| P. value = 0.7, not significant | | | | |

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. The 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 et al. (10), 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's 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) in their 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 >35 years 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). The 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.

The present study is not free of limitations, among these; the study conducted in a single center , short period study and missed to follow up of some participants, additionally, 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. Hence, we recommended advising of infertile couples regarding risks of congenital anomalies after in vitro fertilization, and frequent evaluation and monitoring of pregnant women conceived by in vitro fertilization as an important issue especially for women with multiple pregnancies and positive consanguinity. However, further national multi-centers studies on risk of congenital anomaly in infants born by in vitro fertilization are highly suggested.

Ethical Clearance : The study protocol approved by the Iraqi Ministry of health-scientific committee. Verbal and Signed consents obtained from all patients. Data collection was in accordance with World Medical Association Declaration of Helsinki , 2013, for the ethical principles of researches that involve human. Data kept confidentially and patients privacy were assured.

Conflict of interest: Authors declared none

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