# Risk of birth defects and other childhood adverse outcome associated with *in vitro* fertilization

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## Abstract:

### Background:

*In vitro* Fertilization (IVF) is an important alternative for infertile couples, there is an increase in the number of children conceived by IVF worldwide.

### Objective:

The aim of this study was to assess the risk of birth defects and adverse outcome among infants and children conceived by *in vitro* fertilization in Sulaimani-Iraq.

### Patients and Methods:

This case-control study was carried out on 160 children, 75 were product of IVF(using ICSI) and 85 were product of natural conception. Data collected regarding mother age, father age, duration of infertility before pregnancy with the index child, any complication during pregnancy, age of the child, gender, mode of delivery, gestational age, weight at delivery, history of neonatal admission and it's cause, admission to hospital after neonatal period, and history of surgical operation. All children were examined for any gross anomaly, cardiovascular, respiratory, gastrointestinal, skeletal, urological and neurologic abnormality.

**Results:** IVF was a risk factor for prematurity (OR, 7.844 95% CI 3.025 - 20.339) , LBW (OR, 4.645 95% CI 2.038 -10.587), Congenital anomaly (OR, 1.362 95% CI 0.720 - 2.576), predominance of male gender (OR, 1.340 95% CI 0.719-2.498), neuro-developmental delay(OR,1.333 95% CI 0.672- 2.646), admission to NICU (OR,1.703 95% CI 1.052-2.758 ), C/S delivery (OR, 1.972 95% CI 1.507-2.581), and childhood hospitalization (OR, 1.193 95% CI 0.838-1.696), also there was statistically significant association with multiple pregnancy.

### Conclusions:

IVF carries increased risk of LBW, prematurity, congenital anomaly, neuro-developmental delay, admission to NICU, childhood hospitalization, C/S as a mode of delivery and predominance of male gender.

**Key words:** *In vitro* fertilization, birth defect, adverse out come.

## Introduction:

Assisted conception is the facilitation of natural conception by some form of scientific intervention. It has been available for many years, but one of the first recorded and possibly best known instances of assisted conception was that performed by the eminent surgeon Jhon Hunter, in London 1785.[1]

Children conceived through Assisted Reproductive Technology (ART) comprise as many as 1% to 2% of total births in some countries. High rates of multiple births, with attendant complications of prematurity and low birth weight, are well documented. Concerns are now emerging about associated increased risks for congenital anomalies along with use of newer techniques that may bring additional hazards, especially those requiring more biologic manipulation than artificial insemination and other older ART methods.[2] The aim of this study was to assess the risk of birth defects and adverse outcome among infants and children conceived by *in vitro* fertilization in Sulaimani-Iraq.

## Patients and Methods:

This case-control study was carried out on 160 children, 75 children (cases) were products of IVF using Intracytoplasmic Sperm Injection (ICSI) taken from Dwarozh Center for IVF in Sulaimani-Iraq, and 85 children (controls) were products of normal fertilization without using any assisted reproductive techniques; they were randomly selected from children attending for routine child health supervision in Ali Kamal Center for primary healthcare in Sulaimani, during the period from 1st July 2012 to 30th June 2013. The cases included 14 twins, 1 triplet and 44 singleton children. The controls were all singleton children. After agreement on informed consent for participation, data were collected regarding: mothers' age, fathers' age, gravida, parity, abortion and sibling death, years of infertility before pregnancy with this child, any complication during pregnancy, age of the child, gender, mode of delivery, gestational age, weight at delivery, history of admission to neonatal intensive care unit (NICU) and it's cause, admission to hospital after neonatal period for both, and history of surgical operation. All children were examined for any gross anomaly, cardiovascular, respiratory, gastrointestinal, skeletal, urological and neurologic abnormality.

The Statistical Package for Social Science (SPSS), version 16, was used for the statistical analysis. Independent t-test was used for equality of means; Chi-square and Fisher exact test were used for comparison of contingency tables and Odd's ratio for risk estimation. The results were considered to have a statistical significance when the P values were =or < 0.05.

## Results:

We assessed 160 children from 147 families, in which 75 children were conceived by in-vitro fertilization using ICSI in Dwarozh center for IVF in Sulaimani and 85 were naturally conceived children. Regarding maternal age, paternal age and children age were nearly similar for cases and controls with no significant difference in the means of their age, while for the years of infertility before conception with the index child there was a significant difference (p value < 0.0001) between the mean of years of cases and controls as shown in table (1).

**Table (1) Age of children, parents, and infertility years among case and control**

| Parameters | Cases Mean ± Std. Deviation | Controls Mean ± Std. Deviation | p value |
|---|---|---|---|
| Baby age in month | 18.525 + 15.196 | 16.094 – 13.515 | 0.294 |
| Duration till conception (years) | 7.810±2.6246 | 4.46769 ± 2.80080 | 0.0001 |
| Father age (years) | 35.95±6.495 | 33.65 ± 8.505 | 0.057 |
| Mother age (years) | 29.77+6.495 | 28.93 + 8.392 | 0.394 |

Regarding prematurity the percentage is higher among case than control and there was a statistically significant difference between cases 28(37.3%) and controls 6 (7.1%); P value < 0.000 and odds ratio 7.844 (95% CI: 3.025-20.339) as shown in table (2).

In this study 25(33.3% ) of IVF cases were multiple pregnancies, while for control there were no multiple pregnancies, table (2). which is statistically significant P value < 0.0001 while odds ratio was not applicable.

**Table (2): Risk of adverse outcome in cases and controls**

| Variables | Cases No. (%) | Control No. (%) | P value | Odds ratio | 95% CI Lower | Upper |
|---|---|---|---|---|---|---|
| Premature birth Yes | 28 (37.3%) | 6 (7.06%) | 0.00001 | 7.844 | 3.025 | 20.339 |
| No | 47 (62.7%) | 79(92.94%) | | | | |
| Multiple pregnancy Yes | 25 (33.3%) | 0 (0.0%) | 0.00001 | Not applicable | | |
| No | 47 (62.7%) | 85(100.0%) | | | | |
| Low birth weight Yes | 31(41.3%) | 5(5.9%) | 0.0001 | 4.674 | 2.038 | 10.687 |
| No | 44(58.7%) | 80(94.1%) | | | | |
| Congenital anomaly Yes | 9(12.0%) | 6(7.1%) | 0.212 | 1.762 | 0.720 | 4.676 |
| No | 66(88.0%) | 79(92.9%) | | | | |
| Admission to NICU Yes | 23(30.7%) | 12(14.1%) | 0.010 | 2.703 | 1.052 | 6.758 |
| No | 52(69.3%) | 73(85.9%) | | | | |
| Childhood illness Yes | 24(32.0%) | 21(24.7%) | 0.198 | 1.465 | 0.828 | 3.099 |
| No | 51(68.0%) | 64(75.3%) | | | | |
| Development Normal | 64(90.1%) | 80(94.1%) | 0.205 | 1.923 | 0.672 | 7.646 |
| Delay | 7(9.9%) | 5(5.9%) | | | | |
| Missed | 4 | 0 | | | | |
| Gender Male | 39(52.0%) | 38(44.7%) | 0.223 | 1.370 | 0.719 | 2.498 |
| Female | 36(48.0%) | 47(55.3%) | | | | |
| Mode of delivery C/S | 64(85.3%) | 43(50.6%) | 0.000 | 1.972 | 1.507 | 2.581 |
| NVD | 11(14.7%) | 42(49.4%) | | | | |
| Growth Normal | 69(97.2%) | 69(81.2%) | 0.003 | Not applicable | | |
| Below5th centile | 2(2.8%) | 11(12.9%) | | | | |
| Above95th centile | 0(0.0%) | 5(5.9%) | | | | |
| Missed | 4 | 0 | | | | |

Out of 75 cases, 31 (41.3%) had low birth weight, while 5 (5.9%) of 85 controls had low birth weight with statistically significant difference;( P < 0.000 ).shown in table (2).

In this study; 23(30.7%) cases that were admitted to NICU, while among controls 12 (14.1%) babies were admitted to NICU, with statistically significant difference( P value is 0.010) and odds ratio 1.703 (95% CI: 1.052-2.758)( table 2).Twenty four (32.0%) of IVF cases were admitted to the hospital while only 21 (24.7%) of the controls needed hospital admission, P value 0.198 and OR 1.193 (95% CI: 0.838-1.696) as shown in table (2).Seven (9.9%) of IVF cases had delayed developmental milestones, while 5 (5.9%) of the controls had delay milestones, there was no significant( P value 0.265) difference between the two groups, and OR 1.333 (95% CI: 0.672-2.646), (table 2). Within the cases ;39 (52.0%) males and 36 (48.0%) females. In the controls we had 38 (44.7%) males and 47 (55.3%) females, there was no significant difference between the two groups, P value 0.223 and OR 1.340 (95% CI: 0.719-2.498), table (2).

There was significant difference in the mode of delivery between cases and controls. Among cases 64 (85.3%) children were delivered by C/S, while among the controls 43(50.6%) children were delivered by C/S; P value < 0.000 and OR 1.972 (95% CI: 1.507-2.581) table (2). The study had 69 cases of normal growth that constitute (97.2%) while there were (2) cases below the 5th centile constitute (2.8%), no cases above 95th centile, and 4 cases were missed. In the control group 69 children of normal growth that constitute (81.2%) of the total and (11) children on or below the 5th centile (12.9%) and (5) children on or above 95th centile equaled to (5.9%). P value 0.003 while Odds ratio was not applicable, table (2).

During the period of current study we had 3 deaths among the cases group which constitute (4% of the cases).

All were premature; one was 28 weeks gestational age died on second day of age, the second was 30 week gestational age died on third day of life, the third one was 33 weeks partner of twin pregnancy died in the first day of life.

Among the IVF cases 9 (12.0%) had congenital anomalies, while in controls 6 (7.1%) had congenital anomalies without statistically significant difference P value 0.212, although OR was 1.362 (95% CI: 0.720-2.576), which is regarded as a low risk factor. The types of congenital anomalies are shown in table (3).

**Table (3): Types of congenital anomalies among cases and control.**

| Congenital anomaly | Case N and % | Control N and % |
|---|---|---|
| Single kidney | 1 (1.3%) | 0 (0%) |
| Hypospadius | 1 (1.3%) | 0 (0%) |
| One hyper pigmented patch | 2 (2.7%) | 0 (0%) |
| Micropenis | 0 (0%) | 1 (1.2%) |
| Unilateral polydactyly | 0 (0%) | 1 (1.2%) |
| Bilateral polydactyly | 1 (1.3%) | 0 (0%) |
| syndactyly | 1 (1.3%) | 1 (1.2%) |
| Cavernous hemangioma | 0 (0%) | 1 (1.2%) |
| Club foot | 1 (1.3%) | 0 (0%) |
| Hypo-pigmented patch | 0 (0%) | 2 (2.4%) |
| deafness | 1 (1.3%) | 0 (0%) |
| White hair patch | 1 (1.3%) | 0 (0%) |

## Discussion

In this (case-control) study evaluate the risk of birth defects and adverse outcome among infants and children conceived by IVF in comparison to those who normally conceived

In this study there was a strong relationship between IVF and multiple pregnancy ; P value less than (0.0001) which was statistically significant but we could not estimate the risk rate because our control not contain multiple pregnancy. As there was transfer of more than one embryo per treatment cycle; there were more cases of monozygotic twins with IVF, this was found by Reynolds MA. et al [3]; the same finding was supported by Blickstein I. et al[3] , and Sachter M. et al [4] showed increase in the number of monozygotic twin as the proportion of monozygotic twins from IVF pregnancies is 1% to 2% at first ultrasound, compared with approximately 0.4% of live births from spontaneously conceived pregnancies, This may signify that the etiology of increased monozygotic twins after assisted reproduction is the gonadotrophin treatment rather than in-vitro conditions, micromanipulation, or multiple embryo transfer.

In this study risk of low birth weight was nearly 5 times more in the cases than in the controls and statistically highly significant, this was found in many other studies as Schieve *et al* and [5], in which they found the rate of LBW was slightly higher. However this finding was not compatible with the study done by Kirsten W et.al.[6] They found no association between IVF and risk of LBW.

The risk of prematurity was nearly 8 times higher in IVF cases than in controls this was compatible with other studies [6-9]. The last 4 studies compare the gestational age of singletons and multiple gestations among IVF with those of normal conception. This was related mostly to the multiple gestations and number of fetal heart detected in the first ultrasound as the number increase the gestational age decrease even if finally delivered one baby.

The risk for congenital anomalies was nearly one time higher among IVF cases than controls and statistically not significant, this was compatible with a study done by Anthony et al. [10] that found a small risk of increase birth defect related to maternal factor not to IVF, while other studies found a statistically significant associations between congenital anomalies and IVF as in the

study of Sari K. et al [11], and A.Farhi et al. [12]

In this study there were one time higher risk of male gender predominance among cases, but the difference was statistically not significant, this was compatible with the study of Chang HJ et al. [13] This may be explained by the fact that in embryo selection they involve the transfer of blastocyst (5 days embryo) rather than the cleavage stage (2 to 3 days age embryo) in which this improve uterine and embryonic synchronicity and enable self selection of viable embryos thus resulting in higher implantation rates, and since the selection of transfer on the bases of the degree of cleavage would increase the male embryos as the male embryos divided faster. [13] However, this finding was not compatible with the study of Luke B et al. [14] in which the IVF showed preference of female gender.

We found in this study the risk for neurodevelopment delay was one time higher among cases than controls but the difference was statistically not significant; this was also found by the study of Bjorn B. et al. [15] this study was cross sectional study among infant, toddler and early childhood in comparison with normally conceived children; while the reverse was found by study of Abdel-Latif *et al* [16] that found a high risk of neuro-developmental delay among IVF children, the last study included premature infants product of IVF and compared them with those of same gestational age from normal conceptions.

In this study, there was nearly 2 times higher risk of NICU admission among cases than control and the difference was statistically significant, this was also found by many studies as Sari *et al* [17], Pinborg *et al* [18], and Ombelet *et al* [19], the last study is a retrospective cohort study included both singleton and twin babies of IVF with spontaneously conceived singleton and twin control that matched for maternal age, parity, fetal sex and year of birth.

In this study this may be related to the finding that most of these babies are either multiple pregnancy, premature, low birth weight, in which regarded as risk group, increasing the need for NICU admission. However, this finding was not proved by the study of Neubourg *et al*. [20].This was a prospective study in which they compare an IVF with single embryo transfer with spontaneously conceived singleton.

In this study, the risk of childhood hospitalization was only one time higher among IVF cases than controls but the difference was statistically not significant this was not compatible with many other studies that show high risk of childhood hospitalization in children product of IVF as Bonduelle *et al*, Reija Klemetti *et al* and Ericson *et al*[21-23].

Most of these studies use cohort studies of IVF children at school age or a retrospective studies to a school age children of IVF and found them to need more health service than naturally conceived children of same age. However our finding may be related to young age of our cases, short duration of our study and small sample size.

In this study the growth of IVF children were optimum, so IVF neither considered as risk factor nor statistically significant for abnormal growth this was also found by Emre et al. [24] in which study they follow up children up to 12 year of age, the same result was found by Saunders et al [25] , Tthis study followed up IVF children up to 2 years and use matched control for plurality and gestation, while in a study done by Ceelen et al [26] they found that children of IVF had abnormal growth as they had higher BMI (body mass index) in comparison to control.

The risk of C/S in current work was nearly two times higher in cases than

control and the difference was significant, this was found also by Sallivan *et al* [27] and Gillet *et al* [28]; in the last study they compared the mode of delivery of a term singleton cephalic IVF pregnancy with those of same character whom conceive spontaneously.

The above result and the result in this study may be related to the lower threshold for performing C/S by the obstetricians and the request of mothers for the C/S to deliver a (precious baby).

In conclusion IVF carries increased risk of LBW, prematurity, congenital anomaly, multiple pregnancies, neuro-developmental delay, admission to NCU, childhood hospitalization, C/S as a mode of delivery and predominance of male gender in comparison to control that represents the general population.

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