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CJOG CLINICAL JOURNAL OF OBSTETRICS AND GYNECOLOGY
ISSN 2640-2890

Observational Study

A Genetic study in assisted reproduction and the risk of congenital anomalies

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Abstract

In vitro fertilization is one of the most common and effective procedure for thousands of couples worldwide who want to have a child and are unable to do so for various reasons. Diverse studies show that couples who conceive naturally after one year of trying had newborns with an increased risk of prematurity and low birth weight, compared with couples who conceived before completing one year of trying. Children from assisted reproduction (AR), have a 30% increased risk of prematurity and low birth weight, compared with children from infertile fathers. Regarding the conflicting results the present study aimed to record the frequency of genetic, congenital anomalies in children and adolescents who had examined in the last decade to the Clinical Genetics Clinic of the National and Kapodistrian University of Athens whose mothers had undergone assisted reproduction. The research process was conducted at the "Aghia Sofia" Children's Hospital based in Athens. However, the cases that were studied came from all over Greece. Initially, the researcher recorded the cases that came to the clinic of Clinical Genetics and whose conception occurred after technical assisted reproduction. After telephone communication and the consent of the parents, a live appointment was scheduled. In this meeting-interview all the provisions of the investigation and the protocol were asked and some elements of the medical history of the cases were confirmed. The total sample included 230 children and adolescents. The resulting data were recorded on a printed form/questionnaire. Then, they were registered electronically in the program SPSS 25.0 (Statistical Package for Social Sciences) with a specific unit code for each case/patient, followed by the processing and statistical analysis of the data as well as the recording of the results. The gender of the participants was male for 118 participants (51.3%) and 112 females (48.7%). Mean and standard deviation (SD) of maternal, paternal (at the time of delivery) age was equal to 36.38 (5.94) and 39.94 (6.58) respectively. The observed abdormalities were 35.53% psychomotor retardation, 23.68% facial abnormalities, 23.68% spinal cord abnormalities, 21.05% morphological abnormalities, 20.61% short stature, 19.74% developmental disorders, 19.30% heart disease, 16.67% neurological diseases, 14.47% genetic syndromes, 11.40% genital abnormalities, 8.33% limb abnormalities, 7.46% dermatological abnormalities, 6.14% eye abnormalities, 6.14% hypothyroidism, 5.70% endocrine disorders, 5.26%otolaryngology abnormalities, 2.63% disease of kidney, intestine, 2.19% vascular malformations. Regarding the karyotype chromosome analysis by G-banding technique, from the 230 children in: 24 (10.43%) a pathological result was found, in 158 children (68.70%) it was found normal (46, XX or 46, XY by case) without other findings, while in 48 children (20.87%) the test was not performed for various reasons. Regarding the results of molecular analysis (DNA) from the 230 children, in 50 (21.74%) a pathological finding was found, in 56 children (24.35%) no abnormalities were found and in 124 children (53.91%) no molecular analysis was performed for various reasons. In conclusion, the sample of this descriptive study is characterized as uniform in terms of the method of assisted reproduction since 96.24% had followed the classic IVF. Full-term pregnancy was associated with the appearance of malignancy and head morphological abnormalities (64.6%), normal pregnancy was associated with genetic syndromes (18.2%) and facial abnormalities (11.1%). It is recommended the screening oocyte and sperm donors in order to help protect the safety and health of donors, recipients, and future offspring. The present study confirms the association of the presence of congenital anomalies after *in vitro* fertilization (IVF). However, the absolute risk of developing severe dysplasias after an IVF procedure is limited.

More Information

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Submitted: September 07, 2021
Approved: October 11, 2021
Published: October 12, 2021

How to cite this article: Chrysoula K, Eleni K, Vasiliki E, Dimitrios L, George C, et al. A Genetic study in assisted reproduction and the risk of congenital anomalies. Clin J Obstet Gynecol. 2021; 4: 096-100.

DOI: 10.29328/journal.cjog.1001095

Keywords: Assisted reproduction; Congenital; Children; *in vitro*

Introduction

In vitro fertilization is one of the most common and effective procedure for thousands of couples worldwide who want to have a child and are unable to do so for various reasons [1,2]. Assisted reproduction ensures that couples have their own child and at the same time with the least chance of having congenital and chromosomal abnormalities [3]. The factors responsible for congenital anomalies in children from assisted reproduction have been studied and there is evidence that infertility of the couple plays a role.

Diverse studies show that couples who conceive naturally after one year of trying had newborns with an increased risk of prematurity and low birth weight, compared with couples who conceived before completing one year of trying [4]. The cause of the couple's infertility plays a role, according to Kawwass, et al. [5]. Children from assisted reproduction, whose mothers were unable to conceive due to fallopian tube cyst or other anomalies had a 30% increased risk of prematurity and low birth weight, compared with children from assisted reproduction and infertile fathers. Declercq, et al. [6] studied the risk of perinatal complications in 334628 births in Massachusetts, USA, comparing three groups of women: those in the first group who conceived by assisted reproduction, those in the second group were infertile but conceived naturally, and those in the third group who were fertile. It was found that women in the first group had children with a significantly increased risk of premature birth and low birth weight, while the risk was lower in the group of fertile women compared to the other two groups. These findings are an indication that preterm birth and low birth weight are associated with female infertility and that assisted reproduction increases this risk [6].

Ooki, [7] studied whether the mother's age is related to the congenital anomalies with assisted reproduction. It was found that chromosomal abnormalities per pregnancy and per birth increased significantly with the age of the mother, while, on the contrary, non-chromosomal abnormalities per pregnancy seemed to decrease, with the exception of diverse anomalies which increased significantly. In fact, perinatal congenital anomalies of the nervous system have been shown to decrease significantly with maternal age [7].

Ooki, [8] who studied 2,725 births in Japan between 2004 and 2016, found a significantly higher risk of congenital malformations after intracellular insemination than *in vitro* fertilization. Overall, cryopreservation of embryos was not accompanied by a statistically significantly increased risk of congenital anomalies compared to the other two aforementioned methods [8]. On the other hand, Pelkonen, et al. [9] who included in their study 1830 children from cryopreservation and 2942 children from assisted reproduction without cryopreservation, came to clearer conclusions. They found that there was no significantly greater risk of major congenital malformations, both as a whole and in each organ separately, with the use of cryopreservation [9]. Han, et al. [10] studied 9101 newborns resulting from assisted reproduction between 2004 and 2014: 2919 children from *in vitro* fertilization, 1996 from intracellular insemination and 4186 from cryopreservation. *In vitro* fertilization was found to be associated with a slightly higher risk of congenital anomalies than the other two methods. With regard to cryopreservation, there was a significantly increased likelihood of congenital malformations in multiple pregnancies and in mothers older than 35 years [10]. Yu, et al. [11] studied 6372 newborns from assisted reproduction: 3375 from *in vitro* fertilization and 2997 from intracellular plasma insemination. The percentage of newborns resulting from cryopreservation was 60% and 65% respectively [11].

In contrast, Beltran Anzola, et al. [12], who found, in 2379 fetuses and newborns from assisted reproduction, a rate of congenital anomalies of 4.9%, found no difference in the risk of these anomalies between cryopreserved and non-cryopreserved fetuses [12]. Levi Setti, et al. [13], who compared pregnancies with cryopreserved or non-eggs, found in the second group a higher risk of low birth weight, both in singleton and twins, but no significant difference in the likelihood of congenital malformations [13].

Zhu, et al. [14] included in their study, 18221 children from assisted reproduction, of which 12649 came from *in vitro* fertilization and 5572 from intracellular plasma insemination. In monogamies, the percentage of those who showed congenital anomalies was 1.15% in the first group and 1.38% in the second, while in twins the respective percentages were 2.74% and 2.58% respectively. No significant difference was found between the two groups, in both singleton and twin pregnancies. This difference was also insignificant in cases where cryopreservation was used [14]. Davies, et al. [3], who conducted a study in the Australian population (6163 children), found that there was no increased risk of congenital malformations by IVF, while, on the contrary, a risk was found in children generally from assisted reproduction (8.3% *vs.* 5, 8% in the control group) [3].

Some studies indicate that infants conceived through AR are at higher risk of congenital abnormalities than normal pregnancies, but other studies do not observe such difference or have reported less risk, especially in multiple pregnancies [15]. Regarding the conflicting results this study aims to assess the complications and the risk of some congenital anomalies including cardiovascular, central nervous system, musculoskeletal, urogenital and chromosomal abnormalities in newborns conceived following assisted reproduction methods.

Aim of the study

The aim of this study was to record the frequency of genetic, congenital anomalies in children and adolescents who

had examined in the last decade to the Clinical Genetics Clinic of the National and Kapodistrian University of Athens whose mothers had undergone assisted reproduction.

Methods

The total sample of children and adolescents included in the study was 230 participants. The report of the frequency of abnormalities in children and adolescents who had been conceived through assisted reproduction, concerned incidents that came to the Clinic of Genetics of the National Kapodistrian University of Athens, located at the General Research Laboratory of Children's Hospital "Aghia Sophia" in the last decade. The sampling criteria were as follows:

- The children were conceived through assisted reproduction.
- One of the two parents speaks the Greek language adequately with contact information through their medical record. This research was carried out from studied cases all over Greece. With the consent of the parents, a lifelong appointment was scheduled. With a special questionnaire and interview, all the provisions of the investigation and the protocol were covered and some elements of the medical file of the cases were confirmed. The resulting data were recorded on a printed form/questionnaire. Then, they were registered electronically in the program SPSS 25.0 (Statistical Package for Social Sciences) with a specific unit code for each case/patient, followed by the processing and statistical analysis of the data as well as the recording of the results. Response frequencies (N) and percentages (%) were used to present the qualitative data of the present study. For multiple choice questions the percentages were calculated based on the number of participants and not the number of answers.

Results

Regarding the sex of the children whose conception resulted from assisted reproduction technique, 118 children in the sample (51.30%) were boys and 112 girls (48.70%). Mean and standard deviation (SD) of maternal, paternal (at the time of delivery) age was equal to 36.38 (5.94) and 39.94 (6.58) respectively.

The table 1 shows the total number of observed abnormalities and table 2 the number of donor's ovum and the abnormalities observed in the newborns.

Table 1: Total number of observed abnormalities.

Abdormalities	Number of children	Percent %
psychomotor retardation	81	35.53%
facial abnormalities	54	23.68%
spinal cord abnormalities	54	23.68%
morphological abnormalities	48	21.05%
short stature	47	20.61%
developmental disorders	45	19.74%
heart disease	44	19.30%
neurological diseases	38	16.67%
genetic syndromes	33	14.47%
genital abnormalities	26	11.40%
limb abnormalities	19	8.33%
dermatological abnormalities	17	7.46%
eye abnormalities	14	6.14%
hypothyroidism	14	6.14%
endocrine disorders	13	5.70%
otolaryngology abnormalities	12	5.26%
disease of kidney, intestine	6	2.63%
vascular malformations	5	2.19%
cancer	3	0.0132

Table 2: Frequency regarding the abnormalities in children born after IVFs with donor's ovum.

Diagnosis (Abnormality)	Absolute frequency	Relative frequency (%)
Developmental delay	6	28.57
Congenital cardiopathies	6	28.57
Short stature	4	19.05
Limb anomalies	2	9.52
Cranium-Facial anomalies	9	42.86
Genital anomalies	4	19.05
Otolaryngological anomalies	1	4.76
hypothyrodism	1	4.76
Anomalies of the body	5	23.81
Dermatological anomalies	2	9.52
Vessels dysplasias	1	4.76
Neurological diseases	2	9.52
Other Endocrine abnormalities	2	9.52
Cancer	2	9.52
Genetic syndromes	2	9.52
Total	49	233.33

Discussion

The morphological abnormalities of the face included cleft lip, cleft palate and micrognathia. The cryptorchidism, the hypospadias were included in the genital abnormalities. Eye disorders include diseases such as strabismus, hyperopia, and severe myopia. Otolaryngological disorders include hearing problems such as deafness, and other disorders that are part of otolaryngology. The morphological craniofacial abnormalities included microcephaly, craniosynostosis (such as: triangular head, dolichocephaly, scaphocephaly) and intercostal hypoplasia. Developmental disorders included autism spectrum disorder (ASD), Asperger syndrome, Attention Deficit Hyperactivity Disorder (ADHD), and diffuse developmental disorders (ADHD). Hypothyroidism included functional disorders of the thyroid gland. Various skeletal abnormalities were included in the trunk abnormalities (such as scoliosis, other skeletal malformations, hyperelasticity, osteogenesis imperfecta). Café-au-lait spots, bronze baby syndrome, various dermatoglyphics, atopic dermatitis were included in the dermatological abnormalities. Diseases such as hemangiomas have been implicated in vascular malformations. Neurological diseases included hypotonia, eyelid drop, convulsions, spastic quadriplegia, and fine mobility. Endocrine disorders include disorders due to hormonal problems such as menstrual

disorders, ovarian cysts and hair growth. Various tumors such as Wilms/nephroblastoma were included in the category of cancer. The various syndromes of genetic etiology have been included in the category of "genetic syndromes" which will be studied in more detail. Kidney, liver, and intestinal diseases included enterocolitis, hepatomegaly, solitary kidney, renal failure, and bowel prolapse. Regarding the assisted reproduction technique, three participants did not want to provide information. However, among the 228 participants, there were 30 participants who in the past had made more than one attempt at assisted reproduction technique. The 26 participants (11.45%) had induced ovulation and intrauterine insemination (IUI), 219 participants (96.48%) had undergone *in vitro* fertilization (IVF), and 12 participants (5.29%) had undergone fertilization or otherwise intracellular spermatozoon infusion (ICSI). Of the 30 cases in which attempts were made with multiple assisted reproduction techniques, 28 were by IVF, 1 by IUI and 1 by ICSI.

Regarding the karyotype chromosome analysis by G-banding technique, from the 230 children in: 24 (10.43%) a pathological result was found, in 158 children (68.70%) it was found normal (46, XX or 46, XY by case) without other findings, while in 48 children (20.87%) the test was not performed for various reasons. The results of karyotype testing in children were the following: 46, XYY [86%] (n = 1), 46, XX, 9qht (n = 1), 46, XY, 1qht (n = 1), 46, XX, inv (1) (n = 1), 46, XX, inv (3) (n = 1), 46, XX, inv (9) (n = 3), 47, XXX (31%) (n = 1), deletion of chromosome 18 as 18p11.1-18p11.32 (n = 2), with monosomy X: 45, XO [50] (n = 1), with trisomy 21 (46, XY, + 21) (n = 2), 46, XY [t (5p: 13p)] (n = 1), 46, XX del 20p13; dup 3p26.3 (n = 1), 46, XX [97%]/45, XO [3%] (in a mosaic form)(n = 1), 46 XX + (11; 12) (q21; q14) de novo (n = 2) and DiGeorge syndrome (n = 5).

Regarding the results of molecular analysis (DNA) from the 230 children, in 50 (21.74%) a pathological finding was found, in 56 children (24.35%) no abnormalities were found and in 124 children (53.91%) no molecular analysis was performed for various reasons. Regarding the method of delivery, 17 participants (7.39%) had a normal delivery. In patients born with normal birth, the highest percentage were found to have facial abnormalities (11.1%), eye abnormalities (14.3%), developmental disorders (11.1%) and genetic syndromes (18.2%). In addition, 101 participants (44.30%) had a full-term pregnancy and the largest percentage had dermatological abnormalities (64.7%). In total, 127 participants (55.70%) had a premature birth. The number of weeks completed gestation ranged from 19 to 36 weeks (viable or stillbirth), with a mean of 32.94, a standard deviation of 3.05, a median of 34 and a prevalence of 36 weeks. In patients born prematurely the highest percentage had hypothyroidism (78.6%), morphological abnormalities of the head-skull (64.6%), genital abnormalities (61.5%), neurological diseases (60.5%) and malignancy.

In conclusion, the sample of this descriptive study is characterized as uniform in terms of the method of assisted reproduction since 96.24% had followed the classic IVF. Full-term pregnancy was associated with the appearance of malignancy and head morphological abnormalities (64.6%), normal pregnancy was associated with genetic syndromes (18.2%) and facial abnormalities (11.1%). The present study confirms the association of the presence of congenital anomalies after *in vitro* fertilization (IVF). However, the absolute risk of developing severe dysplasias after an IVF procedure is limited.

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