Bioethical analysis of the impact of Assisted Reproduction Techniques (ART) on the health of children and mothers

Análisis bioético del impacto de las Técnicas de Reproducción Asistida (TRA) en la salud de niños y madres

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Abstract

Assisted reproductive technology (ART) can be connected to obstetric and perinatal complications, including a higher risk of congenital malformations and acquired diseases. It is an important duty of healthcare professionals, to inform those who wish to avail themselves of these techniques, about both the health risks for mother and newborn. Apart from the biological risks, ART also raise bioethical problems that must be addressed through the central value of the human life.

The main aim of this retrospective study is the bioethical and biomedical analysis of the impact of ART on children and mothers' health, comparing the risk of pathology in natural conceived babies, and those who are ART infants.

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1. Introduction

There is no doubt that getting a child for a couple who has difficulties for it, is a good objective. To achieve this, assisted reproduction techniques (ART) or natural methods of regulating human fertility can be used.

The ART has a wide social acceptance, since the first girl, Louise Brown, was born in 1978, due to in vitro fertilization, in the world more than 200,000 children are born per year by these techniques,[1] that is, more than 3% of the children born,[2] the total being more than 8 million.[3]

However, like any biomedical intervention, assisted human reproduction techniques are not risk free. In fact, at the beginning of the 1990s, a pediatric alert began due to the defects and anomalies that those children presented. It seemed apparently, it was in a greater proportion than those born naturally,[4] since numerous retrospective cohort studies demonstrated an increased risk of congenital defects,[5-7] in particular of cardiac malformations and chromosomopathies, associated with in vitro fertilization,[8-9] although others, however, did not detect statistically significant differences when stratifying them according to maternal age, parity and gestational age.[10] In addition, in a recent study that analyzes the long-term health status of children born by ART, no significant differences were not found with those born naturally.[11]

When assessing whether there are differences, regarding the risk of congenital malformations according to the technique used, in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), several studies do not find them,[12-14] although another does show an increase in congenital defects after ICSI, but not after IVF.[15]

Regarding intrauterine insemination, it has also been shown to carry as many risks of congenital anomalies in the offspring as IVF or ICSI.[16]

Regarding the possibility of suffering from acquired pathologies, some studies detect that children born by IVF are at greater risk of suffering from psychomotor development disorders, cerebral palsy, autism[17, 18] and asthma,[19] and in general worse health situation in early childhood.[20] In the longer term, premature vascular aging is detected, with a higher risk of arterial hypertension.[21]

Another aspect that generates concern is the future fertility of people conceived of IVF, since a worse quality and quantity of semen has been reported in young adults born after ICSI, possibly related to the infertility of their father.[22]

About the cause of the problems suffered by children born by ART, it seems to be due to a combination of parental subfertility and the techniques themselves, without losing sight of the greater number of multiple pregnancies that occur in ART,[23] which, as it is known, often present greater problems than single fetus pregnancies.[24]

Epigenetic mutations[25] could also be involved, which could occur mainly during gamete formation, fertilization and the early stages of embryonic development.

As for mothers who undergo ART it has been shown that to be at greater risk of obstetric pathology, mainly due to the ovarian hyper-stimulation syndrome.[26]

This article studies the impact of ART on the health of children conceived by these techniques compared with those born by natural conception (NC), at La Fe University Hospital, in Valencia, Spain, and at the same time, it is carried out a more comprehensive evaluation of the bioethical problems that may accompany ART.

2. Material and Methods

This is a retrospective observational study of cohorts of newborns in 2016 at the La Fe Hospital in Valencia (Spain). Through a simple random sampling, 300 children from natural conception and 300 from ART were selected. In both groups there were approximately the same number of newborns of each sex, although with a slight male predominance, 157 men (52.33%) and 143 women (47.67%).

Exclusion criteria were considered for live births who died subsequently for any reason whatsoever and those born alive without follow-up data in the electronic medical record of the Hospital.

The evaluable variables were maternal age, gestational age, type of pregnancy and number of children. Also, weight at birth, type of delivery, exposure to the mother's toxics and types. Furthermore, it included gestational pathology, fetal distress, family history of genetic diseases, income at birth, congenital malformations and their type (according to the ICD-10 classification), pathology acquired up to 2 years of age and their type (diseases coded in ICD-10 are included, except for infectious pathologies and transient diseases produced totally due to external mechanical factors).

In addition, in the children-ART cohort, the type of technique (conventional IVF, ICSI and Artificial Insemination [AI]), reason for ART (maternal, paternal, mixed factor), and the origin of gametes (own or donor).

Data are expressed as mean (standard deviation), median (1st, 3rd quartile), in the case of numerical variables and by absolute percentage frequency for qualitative variables.

To evaluate the possible differences between the ART and NC groups, multivariable logistic regressions are adjusted. The variables of maternal age, gestational age, toxic and multiparous women are introduced as confounding factors.

To contemplate the non-linear effect of age, third-degree splines are added to the model. Additionally, a linear regression

model is used to assess the association between gestational age and multiparous women. In addition, to log multiparous with ART, a logistic regression is adjusted. All analyses are performed using the R statistical software (version 3.6.1).

3. Results

During 2016, 5292 children were born at La Fe Hospital, of which 4799 (90.6%) by NC and 493 (9.3%) by ART, whose characteristics are specified in Table 1. Data referring to maternal age by Age groups are shown in Table 2.

As for the percentage of caesarean sections, it was 3 times higher in the ART group than in the NC. On the other hand, in the ART group 51% of those born were multiple pregnancies, while in the NC group this percentage was 3.67%. A single triplet was recorded in the NC group, compared to 5.0 in the ART group (Table 3).

Regarding maternal pathology, 17% of the mothers-NC presented some type of gestational pathology, compared to 37% of the mothers-ART.

On the other hand, the percentage of premature children and their characteristics are specified in Table 4. It shows that 6% of ART children had low birth weight, compared to 0.66% of children-NC (Table 5).

In both groups, 3 children were born with loss of fetal well-being at birth. There is also a higher percentage of income at birth in the ART group (28.3%), compared to 6.6% in the NC group.

The percentage of children with a history born to parents with hereditary diseases was likewise other results, higher in ART children (8.33%) compared to 1.33% in NC.

Of the ART-children cohort, 91% were the product of IVF and 9% of artificial insemination (AI). Approximately a quarter of IVF were made through ICSI, although this data is probably underestimated due to a lack of clinical records.

ARTs were performed due to maternal causes in 53% of cases, due to paternal causes in 11% and due to mixed causes in 27%.

Although gametes from their parents were used in the majority of ART-children, more than 30% came from donors.

Regarding medical problems, ART children presented them in 56.67% of cases and 43.33% in the NC group. In the ART group, 19% of congenital malformations were detected, compared with 9.3% in the NC group.

The most frequent pathologies in the ART group were cardiac malformations (24 children), followed by urinary (9 children), musculoskeletal (7 children) and chromosomal abnormalities (7 children).

In the case of the 3 ART-children who presented psychomotor retardation, a genetic study was requested that confirmed the presence of de novo mutations causing the disease. So far, it has had no clinical repercussion, sex being assigned respectively according to internal and external genitalia. The syndromes and chromosomopathies of both cohorts are specified in Table 6.

The frequency of acquired pathology is higher in the group of children conceived by ART (62%), than in the NC group (38%). The most frequent type of pathology is described in Graph 1. No children with oncological or rheumatologic pathology were registered, probably because the incidence of this pathology in childhood usually occurs at ages greater than two years.

It has also been confirmed that at a lower gestational age of children, there is a higher risk of congenital malformations (OR = 0.913, 95% CI [0.844-0.99], P = 0.023), regardless of the age of the mothers, who have had exposure to toxics, which have been conceived naturally or by assisted reproduction techniques. It cannot be said that the greatest risk of congenital malformations in ART-children, is due to the technique itself (OR = 1,459, 95% CI [0.793-2701], P = 0.225).

Regarding the risk of suffering acquired pathology during the first 2 years of life, it is observed that it is increased, in children of

lower gestational age (OR = 0.743, 95% CI [0.669– 0.816], P <0.001). In addition, children conceived by ART have a higher risk of presenting pathology during the first two years of life (OR = 1,926, 95% CI [1,301– 2,857], P = 0.001). (Table 7).

The analysis of the gestational pathology of mothers undergoing ART is a secondary objective of this study, proving that older mothers and those undergoing ART have a higher risk of gestational pathology. In turn, the presence of pathology during pregnancy is also statistically significant related to prematurity (lower gestational age). The older the mothers, the greater the risk of gestational pathology (OR = 5,096, 95% CI [1,371–26.44], P = 0.028). The greater the presence of gestational pathology, the lower gestational age (OR = 0.918, 95% CI [0.856-0985], P = 0.018). Mothers undergoing ART are associated with an increased risk of gestational pathology (OR = 1.97, 95% CI [1,246-313], P = 0.004).

It is also verified, that there is no different risk of presenting gestational pathology (OR = 0.639, 95% CI [0.279 - 1.50], P = 0.294), congenital malformations (OR = 1.62, 95% CI [0.514-7.26], P = 0.458) or Acquired pathology (OR = 0.519, 95% CI [0.191 - 1.27], P = 0.169) in children conceived by IVF with respect to those conceived by AI, controlling the gestational age, maternal age, and toxicity of mothers. There are also no differences between IVF and ICSI techniques, in terms of the risk of gestational pathology (OR = 1,548, 95% CI [0.877- 2,725], P = 0.13), congenital malformations (OR = 1,168, 95% CI [0.561 - 2,346], P = 0.669) or acquired pathology (OR = 1.422, 95% CI [0.794-2593], P = 0.242), controlling the same variables.

Absence of father figure

The children registered without a father figure were 29, almost 10% of the ART cohort. Two of these children had 2 mothers, and the other 27 had mothers without a partner, it should be noted that all single mothers and lesbian mothers used IVF. 55% of these

mothers were over 40 years old when the procedure was carried out. The longest registered single mother was 47 years old.

Approximately half of the pregnancies were twins. The pregnancies of the children with two mothers were single births, so, if we consider only the 27 mothers without a partner, 15 of them (more than half) faced a multiple pregnancy.

In 16 of the mothers, IVF was carried out with donor semen, and in 13 of them, there was donation of both gametes, being the main cause of egg donation, their advanced age (11 of the 13 were over 40 years old).

4. Discussion

The data of this study confirm those previously mentioned in the literature, related to the higher incidence of medical problems in children born by ART.

Nevertheless, in our study, it should be noted that children born by ART have a higher risk of developing pathology up to 2 years of age, than those born by NC, regardless of other factors that may be directly related to their appearance (advanced maternal age, prematurity, multiparous, toxic exposure during pregnancy and gestational pathology). Likewise, these children are at greater risk because they come from multiple pregnancies, which favors prematurity and this in turn constitutes a greater risk of suffering from cardiac, urinary and musculoskeletal abnormalities. They also have a greater number of congenital malformations and chromosomal abnormalities.

Mothers undergoing ART have a higher risk of developing pathology during pregnancy, a risk that is also increased by the more advanced maternal age.

However, no significant differences have been seen between ICSI, IVF and AI.

On one hand, the fact that congenital malformations are more frequently associated with prematurity, and therefore, more present in children born by ART, is a worrying fact, because congenital malformations constitute the first cause of infant mortality (neonatal and post neonatal) in Spain.[27] In fact, more than half of the deceased ART-children, who were excluded from the study, had serious congenital malformations, some incompatible with life.

On the other hand, also in Spain from 2001 to 2016, the rates of neonatal and post neonatal mortality have fallen by 32.1% and 35.1%, respectively.[27] Much of this decline is due to the decrease observed in deaths due to congenital malformations, deformities and chromosomal abnormalities, since they represent almost one fourth of all deaths in children under 1 year of age. Specifically, the infant mortality rate due to this cause of death decreased by 45.1% between 2001 and 2016. If it is taken into consideration, that with the approval of The Organic Law 9/1985, abortion was legalized in Spain under three assumptions,[28] and one of them (the «eugenic» assumption) allowed aborting children with congenital malformations. Subsequently passed, the Organic Law 2/2010, currently in force, which legalized abortion for serious malformations in the fetus at any time during pregnancy,[29] it seems reasonable to think that this has been able to influence the decrease in mortality due to congenital malformations.

Ethical assessment of ART

Regardless of the medical data referred to, above, ARTs also deserve an ethical reflection.

Undoubtedly, the fact that a couple with infertility problems can have a child using ART is a positive good; hence, its great social acceptance. However, it is also objective that, both mothers as well as children born, can show adverse medical effects, as has been observed, both in the results of this work, and in the extensive

literature review carried out; but in addition to this, it is also a reality that when using ARTs, a high number of human embryos are lost.[30]

All this abounds in the need to carry out, even very succinctly, a bioethical reflection on these techniques.

In addition to the already known adverse effects that mothers and children can suffer, and the loss of embryos already mentioned, the ART present other bioethical difficulties. Take for an instance, the excess embryos that are generated to make the technique profitable, which forces freezing a large number of them. This practice undoubtedly, is not in accordance with the human dignity of these embryos. Meanwhile there is also not a reasonably acceptable solution for them, since most of these embryos are used for biomedical investigations that lead to their destruction or, as a lesser evil, they are donated for adoption to couples other than their biological parents, which poses undoubted bioethical problems.[31]

It is also known that, sometimes, preimplantation genetic diagnosis is used to select the best embryos to be implanted and thus try to make the most efficient ART. Although we cannot go deeper into this, it is clear that the use of preimplantation genetic diagnosis is aimed at selecting for health reasons, the embryos that are considered of better quality to be implanted, freezing or discarding the rest, which is undoubtedly a eugenic practice.

Nevertheless, the ART also pose bioethical problems related to the donation of gametes, especially in what refers to whether or not such donation should be anonymous, as this may affect the right that born children have to know the identity of their parents and also, to the right of donors to safeguard their privacy. Both positions have objective reasons to be defended, but hardly can be harmonized with each other.[32]

Another bioethical difficulty that can occur around the ARTs is their use for social purposes outside the good of the children and even the dignity of women. Especially there are two most used

practices, surrogacy and «social freezing». The first one, directly affects both the woman who gestates the children, as well as the children's own good, because with this practice the pregnant woman is reified, using her for purposes other than her own good, and also the child produced, which by being a product can be subject to market laws.[33] These bioethical and moral difficulties make that surrogacy be prohibited in the vast majority of countries.

As for «social freezing», a technique that offers women freezing their eggs when they are young, to use them later by going to the ART and thus preventing them from becoming pregnant at an age in which it is assumed that motherhood can be an obstacle to the development of their professional careers.[34] Naturally, this practice also reifies women, subjecting them to labor and economic interests outside their own good, while increasing the risk that pregnancies have at a late age, and deprives children of having young parents, with security more apt to exercise their paternal functions.[34]

Finally, ART can also be the object of a commercialization outside the most basic ethical standards in the doctor-patient relationship, when «deceptive propaganda» is used to obtain clients. We have dealt extensively with this topic in an article that shows how many assisted reproduction clinics present results of pregnancies and children born, not consistent with their reality, to show greater effectiveness and thus be able to increase the huge economic benefits of these clinics.[35]

Limitations of the study

The main limitation of the study is that, since it is a retrospective study, there may be a loss of data not recorded in the clinical history.

In addition, it is possible that the ICSI registry is undervalued because in many mothers, IVF has been carried out in another center other than the birth center, and the method used is not always

specified in their clinical histories. For the same reason, other data, such as the use of preimplantation genetic diagnosis and fetal reductions, have not been collected systematically, as they are not explicitly stated in all the clinical histories.

The methodology of inclusion of patients can also be considered a limitation, because by this being a tertiary hospital, an increase in the incidence of gestational and pediatric pathology can be given, for it is a center where cases of greater complexity and risk are referred. However, these differences also affect the two patient cohorts, so it should not alter the internal validity of the study.

5. Conclusion

This article shows how children born by ART, according to our own results, as well as those in the literature, present more medical problems than those born by NC, especially low birth weight and prematurity, with the clinical consequences of short and medium term that entails. Mothers who resort to these techniques also have a pathology during pregnancy in a greater proportion than in natural gestations; above all, a higher rate of multiple pregnancies, which, as is known, implies a higher perinatal and obstetric risk.

All these medical problems cause the ART to raise objectives bioethical dilemmas, both for themselves, and for being used for purposes beyond the good of the mothers and their children, problems that we have succinctly reviewed in this work.

Tables

Table 1. Description of the cohorts according to maternal age, gestational age and birth weight.

Variable	NC Group (n = 300)		ART Group (n = 300)	
	Average (Mean) (SD) / n (%)	Median (1st, 3rd Q.)	Average (Mean) (SD) / n (%)	Median (1st, 3rd Q.)
Maternal Age	32.62 (5.04)	33 (29, 36)	36.92 (4.76)	37 (34, 40)
Gestational Age	39.07 (2.14)	39.57 (38.29, 40.43)	37.11 (3.37)	37.86 (35.57, 39.71)
Birth Weight	3177.08 (581.78)	3200 (2900, 3572.5)	2686.73 (762.33)	2770 (2232.5, 3271.25)

Table 2. Comparison by maternal age.

Maternal Age	NC(n = 300)	ART (n = 300)
<35	185 (61.6%)	85 (28.3%)
35-39	92 (30.8%)	134 (44.6%)
>40	23 (7.6%)	81 (27%)

Table 3. Comparison of type of delivery, parity and number of children in both cohorts.

Variable	Category	Group NC (n=300)	Group ART (n=300)
Type of birth	Vaginal	237 (79%)	105 (35%)
	Cesarean Section	63 (21%)	195 (65%)
Parity	Single	289 (96.33%)	147 (49%)
	Multiple	11 (3.67%)	153 (51%)
Nº of children	1	289 (96.33%)	147 (49%)
	2	10 (3.33%)	148 (49.3%)
	3	1 (0.33%)	5 (1.67%)

Table 4. Comparison by gestational age groups.

Gestational age (weeks)	NC (n = 300)	ART (n = 300)
<28	1 (0.33%)	12 (4%)
28-32	7 (2.3%)	10 (3.33%)
32-36+6	19 (7.8%)	91 (30.3%)
37-42	273 (91%)	187 (62.3%)

Table 5. Comparison of birth weight according to classification according to gestational age (EG). PEG (small), AEG (adequate), GEG (large).

Somatometry at birth	NC (n=300)	ART (n=300)
PEG	2 (0.66%)	19 (6.3%)
AEG	289 (96%)	278 (92.6%)
GEG	9 (3%)	3 (1%)

Table 6. Comparison of known syndromes and chromosomopathies of both cohorts.

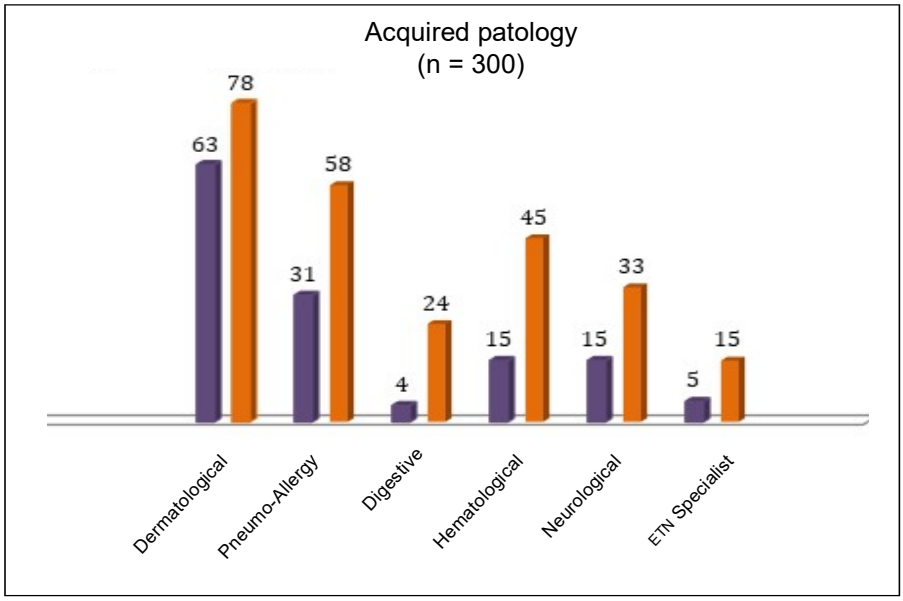
SEX	GROUP	Syndrome Group or Chromosomopathy	Psychomotor Retardation	Gamets
Male	NC	Syndrome Nance-Horan	Yes	Own
Female	ART	Syndrome of Angelman	Yes	Donor semen
Male	ART	Deletion cr.1p34.2	Yes	Own
Female	ART	Chimeras Karyotype: chi 46, XY [18]/46, XX [17]*	No	Ovum-donor
Female	ART	Clinical suspicion of Cook syndrome, genetic slope	No	Both donors
Male	ART	Balanced Translocations. Karyotype 46, XY t (2: 4) (p13, q33)	No	Own
Male	ART	Chimeras Karyotype: chi 46, XY [11] / 46, XX [14] *	No	Ovum-donor
Male	ART	Deletion cr.22q11.22	Yes	Own

* [ ] Number of metaphases found from each cell line.

Table 7. Logistic regression model to analyze the relationship between acquired pathology and ART, adjusting maternal age, gestational age, toxic, congenital malformations and gestational pathology.

Variables	Standard Error	OR (Odds Ratio)	Lower .95.	Upper .95.	P value
Maternal age	0.464	1.102	0.448	2.779	0.834
ART Group	0.2	1.926	1.301	2.857	0.001
Mothers' toxic	0.39	1.516	0.707	3.299	0.286
Congenital malformations	0.263	1.141	0.682	1.918	0.617
Gestational pathology	0.205	1.328	0.889	1.989	0.167
Gestational age	0.039	0.809	0.747	0.871	<0.001

Graphic 1. Comparison of the most frequent acquired pathology.



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