

**THE PRICE OF THE "MIRACLE" OF BIRTH BY
ASSISTED FERTILIZATION TECHNIQUES**

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Assisted Reproduction Techniques (Ovarian stimulation, Insemination, traditional *in vitro* fertilization, FIV, or the injection of a sperm into the ova's cytoplasm, ICSI) have gone, in something more than 30 years, from being a "provisional solution to sterility" because of Fallopian tube obstruction, to a subjugation of procreation to the technical and the economic power with implementation programs. In these programs, family relationships are forgotten and destroyed.

They have been taken out of the stable sterile couple's scope with a logical and profound suffering, and have opened up to lone females, to women with an advanced age, same sex couples, etc. The pretension of this biotechnology is not to merely solve the existing fertility problems. It tries to eliminate the natural limits of female fertility, to try to achieve to free women from gestation, generate children of design through the implementation of the genetic diagnosis prior to implantation, etc. It is not surprisingly then that the programmers of election of which embryos can or cannot be born according to their characteristics complain that they do not progress in the task of devising those futuristic designs because they do not know what child model future progenitors will desire.

The desired child has been converted into *property*, in the dynamics of what can be entrusted, selected and because of it also rejected, due to the strong social perception created that a right for all exists, as a couple or on your own, for the *perfect child*.

It deals with a human experimentation that is measured in efficiency terms of pregnancy that changes the protocols to the rhythm of the damages that are produced and with insufficient prior studies in animals. The main principal technical problems -the treatment for ovarian stimulation, gamete handling and the culturing of embryos, its conservation in cold, the number of embryos to be transferred, and its correct implantation in the uterus-, continue without finding the definite solution. Against fertilization and the start of its development in its natural medium, artificial reproduction undermines the natural environment that it needs.

Meanwhile embryonic and neonatal mortality does not decline and alarmingly increases the health defects of those who are born, in the short and long term. Part of the defects generated by the techniques, that force the spermatozooids and ova that can be defective to fertilize, are inherited. In addition, acquired defects are inherited by the essential handling of the ova, the *in vitro* culture, or by freezing-thawing. In such a way has this happened that the massive use of this technology has created a serious intergenerational problem.

The amount of pregnancies by ovarian stimulation cycle is still around 25-30%. The efficiency is very dependent of the female's age. The delay factor in having the first child and the hormonal disruptors of the environment, that affect the spermatozooids, has made infertility grow rapidly due to the state of the gametes. The techniques are incapable of curing infertility and only bypass with them natural selection, allowing a grave problem to grow without possible solutions in sight.

Countries that use the techniques increase, the number of Centers that carry it out and the number of cycles and patients that resort to it. Some secondary aspects of the protocols have improved. However, the percentage of children born healthy and without problems in the short and long term, have not increased proportionately.

These techniques present, in turn, risks for the female's health, especially because of ovarian stimulation treatment. The emotional impact of the progenitors usually is more intense than in natural procreation. Depressive and anxiety states of women who have submitted to them have been analyzed. It is not ignored that a considerable amount of couples have achieved in this way the happiness of having their own child. Even so, with great frequency the shadow of lost offspring, or thrown away in the process, follows them, and not a few times are present in the health problems of

the mother and of the children.

The negative effects are known on the health and emotional instability of the couple when the gametes of a donor intervene or when a sole female chooses for her child the single parent family model that these techniques give access to. No one ignores the grave psychological problems of biological orphans. There is a growing opinion that those born by assisted reproduction should be informed that their conception was carried out through the donation of gametes. The negation of the knowledge of one of genetic parents can have psychological consequences for the children that can feel deprived of the information needed to develop their identity in the broad sense given the importance of genetics.

However, very few parents talk to their children about their conception by a donor. The reasons being their desire to protect the children from the anguish of not being able to obtain any information on their biological father and, on the other hand, wanting to protect themselves from the potential rejection of the child, or the social stigma associated with male infertility. Notwithstanding, the secret seems to be prejudicial for them, so much physical as psychosocially, and have a negative impact in the internal dynamism of the family.

According to the studies carried out, sole mothers are also worried about the anonymity of the donors of the conception since they believed that their children would need to know them for their psychosocial development, in particular during adolescence. They are afraid that genetic disorders would appear and not have security to the access of genetic information when it is necessary and, also, because they fear the possibility of marriage between siblings.

Unlike the single woman inseminated who assumes the responsibility of bringing up the children on her own, lesbians desire to share the maternity experience. This is that instead of their partner being a mere spectator, by which shared maternity has been initiated where the ovum of one will be fertilized by a male sperm and the other contributes her womb to gestate the offspring in whose inception both have participated. Obviously this is only possible from the legal point of view in countries where, like Spain in 2005, homosexual couples rights, including reproductive, were equated with those of heterosexual couples (Law 13/2005).

The possibility of resorting to surrogate motherhood arose in the framework of assisted reproduction for women who suffered from a uterine pathology. Lending the womb initially was seen as an altruist gift. Later on, it began to be admitted and justified that it should be associated with an economic benefit.

In a third stage, this gestational service has gone on to be a new form of feminine slavery. During the pregnancy, a community of life is created so deep, and intimate that it generates a bond of affective and emotional attachment of such strength that it takes her to feeling as a mother. The uterine mother is condemned to living those months from a merely functional perspective, with indifference and with the intention of abandoning it and not as an event that fully concerns her. In fact, more than 10% of uterine mothers need therapy to overcome the acquired obligation of giving it up at birth. In addition, no one can foresee the consequences of a process such as this can have on the psyche of the child, that one day will know that it was the object of a contract.

We provide here the information from current scientific literature about the state of the techniques and their tendencies. It seems essential to reexamine and contribute complete and thorough information, not only those that go there for their utilization but to society.

The thorough knowledge of what occurs can potentiate the medical politics of the transmission of life. It can make it possible to potentiate the investigation on the cure of sterility, passing through a

precise diagnostic of their causes. It can do more to impede that so much the deterioration of the environment, like the working policies that are one of the causes of the delay in maternity, keep increasing masculine and feminine infertility.

Abstract

Assisted Reproduction Techniques (ART) is indeed a paradigm of human experimentation. It does not meet the scientific requirements or ethical requirements. Moreover, it has created a serious intergenerational problem. They were accepted, despite being very invasive and costly, as a shortcut in the struggle fight infertility due to physical causes, such as obstruction of the fallopian tubes, exclusively based on retrospective research and previous animal studies grossly inadequate. The risks are associated with multiple embryo transfer, risks to the health of the patient who demands treatment, and risks to the offspring. In addition, risks associated with future parental relationships, familiar and fraternal. The main technical problems, treatment for ovarian stimulation, gamete handling, culturing of embryos, their cold storage, the number of embryos transferred, and adequate implantation of the uterus, have not found an appropriate final solution and do not help to lower embryonic and neonatal mortality. As an attempt to solve some of these problems, a resource has been approached: egg and sperm donation, or transfer the embryo or embryos to another woman so that she becomes pregnant. This way, ART has been removed from a field of sterile and stable partners and is now open to single women, older women, same-sex couples, etc. We report here the present knowledge about the state of ART and what the future program prepares. The available data show the need for a serious re-examination; it is essential to publicize the results, and not only to those intending to use it, but to society.

Key words: assisted reproductive technologies, ovarian stimulation, egg and embryo freezing, surrogacy, psychological damage.

1. Where artificial transmission of life is heading towards

In more than 30 years, from a provisional solution to sterility it has gone to a problem of public health, which affects the following generations. Moreover, the indication to apply this technology was, in the beginning, that there was a simple physical obstacle to the encounter of gametes without anomalies: the obstruction of the Fallopian tubes.

In July 2008, the thirtieth anniversary of Louise Brown's birth, the first girl born by in vitro fertilization (IVF), the magazine *Nature* dedicated a special issue to Artificial Reproductive Techniques (ART). In one of Helen Pearson's articles¹, she interviews several pioneers of the development of this technology (Alan Trounson, Miodrag Stojkovic, Scott Gelfand, etc.) about the expected impact of the next thirty years.

The responses assume, without any embellishment of any type, that the pretension of this biotechnology is not merely to amend the fertility problems posed. It deals with eliminating the natural limit of feminine fertility, achieving to liberate women from gestation, generate children of design through the implementation of pre-implantation genetic diagnosis (PGD), etc. There is even a complain about the programmers not advancing in the task of outlining these futuristic designs² because they do not know what model of child the progenitors of the future will wish for. For the moment, and possibly for a long time to, only those embryos that present some type of genetic error or predisposition, that it is known that the family of one or both progenitors can transmit, and select those that interest their characteristics in pro of third parties.

¹ Pearson, H. «Making babies: the next 30 years». *Nature* 454, 2008, 260-262.

² Editorial del 17 Julio de 2008. «Life after SuperBabe». *Nature* 454, 253.

In the more than thirty years that have passed, there is a strong social perception that a natural law exists for everyone, as a couple or on one's own, for the *perfect child*. This, in turn makes the perception of a supposed imperious duty of health professionals of making these desires possible, through whatever type of intervention, and be whatever the health consequences and for familiar and social relations.

Some of those interviewed showed doubts about the security of the procedures by the fact that every time it is clearer the negative effect on the health of the children generated by the implementation of the techniques. However, until very recently they have obviated such a serious matter with the fallacy that the cause is not clear in that it is not known -it was said- what proportion of damage is due to the situation of the gametes of the progenitors with fertility problems and what proportion of the risks is due to the techniques itself.

The investigation about the biomedicine of infertility, diagnosing and intervening in their causes, has progressed very little in comparison with other medical specialties, precisely by having opened this peculiar via of palliating sterility without curing it, which necessarily involves gamete and embryo handling and hormonal treatment of the woman.

It deals with a human experimentation that does not look for possible benefits for the embryo itself but the efficiency in terms of a pregnancy attained. The human subject where the ART acts on is exactly on the embryo that is generated from human gametes, to give a technical response to the desire of a child of a couple, or of one sole person. This is they are considered “patients” to those people that desire a child without engendering it, while it eludes all responsibility on the loss of embryos, the embryos remaining, or the health, in short or long term of those that are born. It is striking regarding this, that in the protocols and in the laws “the patients” are the progenitor/progenitors and only when it deals with comparing amongst themselves the state of fresh embryos with frozen embryos both types of embryos acquire then the character of patient.

The dazzle by biotechnology, the blind trust in scientific-technical progress and above all the eagerness of autonomy on the own corporeality made it forego the transmission of life, the paternal-filial relationship, is one of the *serious* questions of life. Those questions where what is biological and what is personal intrinsically blended in each person, is impossible of disuniting without violating nature. The pretension for opting for processes that require jumping the natural barriers, strengthened in the evolution process, tackles with the reality of the perfect harmonious regulation of natural processes that makes it very difficult to be manipulated.

As severe as that results in the logic of a “production” what matters above all is having enough number of embryos to select among themselves the best, given the normal difficulties expected in accordance with the quality of the gametes from which it splits off.

The economic movement of this technology is very high³. It is also discussed, the convenience or not, in the global age of employing interventions of low economical cost to deal with infertility in countries with few economical resources and that at the same time are applied to birth control programs⁴.

It is accepted, in the first place in Spain, the petition of same sex couples⁵ as a new indication of

³ Griffiths, A., Dyer, S.M., Lord, S.J., Pardy, C., Fraser, I.S., Eckermann, S. «A cost-effectiveness analysis of in-vitro fertilization by maternal age and number of treatment attempts». *Human Reproduction* 25, 2010, 924–931.

⁴ Pennings, G., de Wert, G., Shenfield, F., Cohen, J., Tarlatzis, B., Devroey, P. ESHRE Task Force on Ethics and Law including. «Providing infertility treatment in resource-poor countries.» *Human Reproduction* 1, 2009, 1–4.

⁵ Dondorp, W.J., De Wert, G.M., Janssen, P.M.W. «Shared lesbian motherhood: a challenge of established concepts and frameworks». *Human Reproduction* 25, 2010, 812–814. Marina, S., Marina, D., Marina, F., Fosas, N., Galiana, N.,

ART. On the other hand, it is doubted if they are apt to participate in the ART process women with obesity⁶ that affects the IVF results although not the quality of the embryo⁷. Meanwhile, it is offered to women to enter a program, with more than doubtful results, in order to be able to choose when they feel it is opportune to be mothers storing their ovum in cold storage.

Reproductive “eternal youth” in women is nothing more than science fiction. Premature orphans of aged mothers do not matter? Where is the interest of the child that is born in a confusing family environment deliberately exposed to psychological risks? Where is the child's interest that is born in fragile conditions or that have to be able to tolerate likely side effects whose risks are not evaluated sufficiently.

2. Brief history of the implementation of Assisted Human Reproductive Techniques

In Annex 1, the main articles that show the milestones and steps of investigation, always retrospective, of the implementation of ART in humans are gathered.

Currently in the ART group, some varieties are included:

- 1) *In vitro* fertilization with the transfer of embryos (IVF or FIVET), their variant also *in vitro* consisting in the injection of one sole sperm (ICSI) or the masculine gametes in diverse states of maturing, directly to the cytoplasm of the ova. It is useful when you count on with semen samples with very few spermatozoids, or with immobile sperm or with little capability of fertilizing of it were utilized in the conventional technique of IVF. Later on, it has routinely generalized its use comprising more than approximately 50% of the processes.
- 2) Artificial insemination with the couple's semen or of the donor's.
- 3) Ovarian stimulation that accompanies whatever of the varieties⁸ of assistance.
- 4) A very little used technique is gamete intra-fallopian transfer (GIFT) -based on the simultaneous collocation of the ova and sperm in the Fallopian tubes -whose use is very limited since it is a more expensive procedure and technically more complicated than the *in vitro* fertilization techniques, and the results obtained are not better. Moreover, barely do they speak about zygote intra-fallopian transfer (ZIFT).
- 5) Another variety where the cytoplasm is transferred from one ovum to another has been tried in women who have suffered several failures of IVF due to a defect in the quality of the ova brought about because their mitochondrias do not produce sufficient energy. It was thought that the cytoplasm injection of a healthy donor would rejuvenate the ovule⁹. More than 30 children have been born with the use of this technique. However, the fact that the cells of the children contain mitochondrias of the donor and of the mother has aroused suspicions about the security and resulted rather preoccupying the fact that two of every seventeen fetuses have an abnormal karyotype¹⁰.

The protocol of the *in vitro* fertilization techniques require the obtaining of the ovules through the

Jové, I. «Sharing motherhood: biological lesbian co-mothers. New IVF indication» *Human Reproduction* 25 (4), 2010, 938–941.

⁶ Pandey, S., Maheshwari, A., Bhattacharya, S. «Should access to fertility treatment be determined by female body mass index?» *Human Reproduction* 25, 2010, 815–820.

⁷ Bellver, J., Ayllon, Y., Ferrando, M., Melo, M., Goyri, E., Pellicer, A., Remoh, J., Meseguer, M. «Female obesity impairs *in vitro* fertilization outcome without affecting embryo quality». *Fertility and Sterility* 93, 2010, 447–454.

⁸ Guzick, D.S., Carson, S.A., Coutifaris, C., Overstreet, J.W., Factor-Litvak, P., Steinkampf, M.P., Hill, J.A., Mastroianni, L., Buster, J.E., Nakajima, S.T., Vogel, D.L., Canfield, R.E. «Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network». *New England Journal of Medicine* 340, 1999, 177-183.

⁹ Shoubridge, E.A. «Asexual healing». *Nature* 461, 2009, 354-355.

¹⁰ Barrit, J., Willadsen, S., Brenner, C., Cohen, J. «Cytoplasmic transfer in assisted reproduction» *Human Reproduction Update* 7, 2001, 428-435.

aspiration of the content of ovarian follicles after undergoing a hormonal stimulation in the female. A stimulation that is necessary in whatever of their ART variants.

On the other hand, the ovules have to be mature and their capability for fertilization demands an *in vitro* incubation in controlled conditions, together with the spermatozoids. These are prepared, also for ICSI, in conditions capable of inducing the empowerment: a physiological activation necessary for fertilization.

The multiple transfers of embryos are justified to facilitate the survival of some of them that will be able to nest in the uterus. This measure has been answered by physicians given that the possible multiple pregnancies not only are a danger for the mother but have resulted in a deficit for the children that are born prematurely.

The conditions of the culturing medium of the embryo before its transfer to the uterus has gone on improving when experimenting with the results; they have looked for the characteristics most similar to the natural situation and recently it has been opted for a culturing medium progressively changes with the development of the *in vitro* embryo.

Besides, it has been deemed necessary to freeze embryos during a brief time, in order to connect the state of its development to the maternal biological cycle that will receive and gestate it, or to repeat the embryonic transfer before the failure of implantation of the first embryos of the same cycle, transferred to the uterus. Since the year 1987 various diverse works on the vitrification (fast freezing) in the *in vitro* fertilization processes. They showed the survival of 61% and based on 92 embryo transfers, resulted in a pregnancy rate of nearly 10%. An article of the year 2002¹¹ showed that vitrification may be more favorable than slow refrigeration. This other form of slow freezing is controlled by the computer with which it has, first and foremost, been used. This is done in such a way that the old vitrification appears as a “recent” technique. It was surprising then that the manufacturers of sophisticated freezing machines sponsor numerous workshops, reunions, lectures, and publications, to promote their products, while the vitrification did not need those machines. Once more, commercial interests play down the necessary rationality of the investigation which does not pose the question what is better but what is easier.

The clinical practice of the different forms of IVF is very aggressive to make up the natural inefficiency of the gametes and artificially *forces* its fertilizing capability with which the embryos present a high rate of deficiencies and very low viability. It involves, therefore, a high loss of human embryos. Additionally, it entails the lack of ethics of the investigation that assumes rehearsing to a great scale in humans, without the sufficient prior investigation in animal models. The recommendations to use one or the other procedures and the decisions to this respect are made on the bases of the statistical results *a posteriori*.

Thus, although some secondary aspects of the protocols have improved, it still cannot be taken into consideration, in a thorough manner, all those essential processes in the transmission of life.

2.1 Actual state of ART implementation

The European register of the “*European Society of Human Reproduction and Embryology* (ESHRE),” publishes each year the state of ART in the centers belonging to the diverse European countries that contribute the results. In Annex 2 a relation of Reports are given. In 2012, the 10 years are reached since the introduction of these practices of Pre-implantation Genetic Diagnosis

¹¹ Kuleshova, L.L., Lopata, A. «Vitrification can be more favorable than slow cooling». *Fertility and Sterility* 78, 2002, 449–454.

(PGD)¹² that have generated numerous and grave problems for the selection or elimination of the embryos for its characteristics and that are included in Annex 2.

The publications carried out in each one of the last years, the same as the registers of other countries -USA, Canada, Australia-, show a considerable increase of the number of fertilization cycles. This is not only due to the progressive incorporation of countries to the register of the results of their Reproductive Centers but to the intensification of the processes in the Centers. It is also observed a greater handling of the ovules in the laboratory and in some years, data is included of the husband's insemination or of a donor. The success is still very dependent on the woman's age and increases with the resort of donors. However, the percentage of children born, healthy in the medium term, has not increased proportionately.

Indications exist of limiting to a maximum of two the number of embryos transferred, due to the evidence of the risk of preterm infants and the greater mortality of the offspring whose non-compliance, at times, is "solved" with embryonic reduction, eliminating the uterus of the gestating woman, the excess of fetuses in development.

The number of pregnancies by cycle continues to be around 25-30%. Although the number of embryos in general that are transferred simultaneously has decreased, various embryos are still transferred and, however, the almost totality of births are of a sole baby.

The situation of Spain has become striking, in a series of aspects, regarding the rest of European countries. We take as an example the register of 2009 because it gathers aspects that are missing in others. Thus, even in 2009, data is not contributed from a great part of the existing centers. In Spain 10% of all the cycles of Europe are carried out (41,689 of 418,111). The proportion of traditional IVF versus those conducted by intracytoplasmic sperm injection (ICSI) is very inferior in Spain; this variant of IVF, indicated for masculine infertility, generates more problems for the child's health, precisely because of the limitations of the spermatozooids.

On the other hand, the advanced age of the woman is a principal factor in the failure of the techniques for which people turn to young donors of ovules. Of the 11,475 cycles with ovule donors 5,875 are from Spain. And to Spain corresponds 1,960 cycles with pre-implantation genetic diagnosis (PGD), of the 5,846 cycles in European centers. Despite the multiple indications of transferring two embryos at the most, and even better one, it is still the highest percentage of cycles with up to three embryos: a 37.7% against 21.5% globally.

Spain achieves a higher percentage of pregnancies by transfer conducted (38.8% against 30.3% of the total in Europe) and, however, the percentage of births by transfer is strikingly the lowest (12.1%) in Europe, and inferior to the average, even if the ovules have been donated by young women.

Spain has conducted 107 of the 436 embryonic reductions of all of Europe. Lastly, it is well-known that ovarian stimulation treatment has risks¹³. Some women, approximately 1%, present the hyper-stimulation syndrome. In Spain 183 cases have been produced of the 3347 of the total of Europe.

In this article, we will solely occupy ourselves with the technical problems of these processes aimed at achieving a pregnancy and that this reaches term. The health problems of those born by the use of this technology, is dealt with in the following Report.

¹² López-Moratalla, N., Lago Fernández- Purón, M., Santiago, E. «Selección de embriones humanos. Diagnóstico Genético Preimplantación». *Cuadernos de Bioética* 75, 2011, 243-258.

¹³ Källén, B. «Maternal morbidity and mortality in in-vitro fertilization». *Best Practice & Research Clinical Obstetrics and Gynaecology* 22, 2008, 549-558.

3. A serious scientific objection to the implementation of the ART: a systematic and Voluntary ignorance of the Biology of reproduction

Molecular Biology has had since the end of the last century a great change of paradigm. *Epigenetics* barges in and with it a series of certainties, some of which are essential to carry out rationally the implicated processes in ART. We focus here on the effects of the state of gametes and the consequences of the alteration of said state, by the handling that the *in vitro* will be subjected to, outside its natural medium.

The *central dogma* of the inheritance according to which only transmitted to the descendants is the sequence of bases of DNA of the paternal and maternal chromosomes were obsolete. Apart from this genetic inheritance, the first level of information, other information is transmitted, epigenetic information that regulates the anterior¹⁴. This second layer of information consists in the progressive modifications of the structure and organization of the specific DNA regions, that leave the genes open or closed that can express the message that it contains. This layer of information is created during the process of formation and maturation of the gametes, gametogenesis, and its apparition is totally dependent on the medium where it is carried out.

The epigenetic reprogramming that is conducted in the germinal cells is very drastic and at the same time highly efficient, since it directs and facilitates a stable cellular differentiation during embryonic development¹⁵.

The characteristics, the phenotype, of the resulting individual of the fertilization of the ovule and the sperm of its progenitors, depending on the inherited genetic patrimony that not only includes the first layer, the genes or the genome, but that also includes the second: the state of DNA of each of the gametes. The first layer of the inheritance is identical in the diverse cells that form the organs, the tissues, or systems of the organism. If it changes during the life of an individual the DNA sequence a *mutation* is generated whose consequences are null or that will affect that same individual, depending that the mutation affects a gene or not, or its regulation. Only if the mutation affects a gene in the gametes, that mutation will pass on to the descendants being able to give way to hereditary diseases.

Thus, the *epigenome* state of the gametes is not immutable but, on the contrary, is subject to the environmental changes during the genesis of the feminine or the masculine gamete from the cells of the germinal line, in the body of the female or of the male. They are epimutations with a great influence in illnesses of the descendants. *Epimutations* are environmentally sensible: they change the gene expression in response to the factors of the environment, so much so inferior (as the hormones and the levels or the state of the immune system) as the exterior (toxics of artificial culturing mediums for the maturation of the gametes).

In what now respects we find two consequences. In the first place, the changes of states of the gametes with the handling, that directly affects the embryo generated by the use of ART, especially but not only, in its development stage and during the perinatal period. In the second place the effect on fertilization of the following generations.

During gametogenesis, reprogramming of certain regions of DNA takes place. The most important is carried out by a process of methylation of the cytosines (one of the four bases of DNA) that

¹⁴ Waddington, C.H. «Epigenotype». *Endeavour* 1, 1942, 18-20.

¹⁵ Bonasio, R., Tu, S., Reinberg, D. «Molecular Signals of Epigenetic States» *Science* 330, 2010, 612-616.

occupy specific positions in the regulatory zones of the expression of some genes. These genes denominated *genes with imprinting* have to suffer epigenetic reprogramming in the germinal line, the cells that give way to the gametes, and are necessary for the normal development of the embryo. The screening, that is different in the paternal and maternal chromosome of each pair¹⁶, assumes that the embryo can only use one of the copies during the first stages of its specific development, or the paternal, or the maternal. The deregulation of the genes with imprinting involves disorders of the placenta growth and the intrauterine growth of the embryo.

3.1 Ovogenesis

ART involve ovarian hyper-stimulation for which they apply exogenous gonadotrophins with the aim of stimulating the ovary and producing the greater number of mature oocytes to be produced and fertilized *in vitro*, or to permit insemination. Several processes that occur in the oocyte cytoplasm are required for its correct maturation, the capacity of fertilization and posterior embryonic development¹⁷, if it is fertilized. Ovarian stimulation can delay embryonic development and increase fetal loss¹⁸. To a certain extent, the epigenetic changes of the ovules in ART processes are responsible that in 70% of the cases the desired pregnancy is not achieved.

On the other hand, a specific state of the oocyte is required for it to awaken and enter, in the adequate moment, in the natural cycle of maturation hormonally conducted. This process is regulated perfectly.

Therefore, an alteration that does not control the moment of maturation causes feminine infertility, in women with premature ovarian failure.

On the other hand, the methylation pattern of the oocytes changes progressively with the woman's age and give way to the drastic decline of feminine fertility¹⁹.

3.2 Spermatogenesis

The correct natural process of generation and maturation of the spermatozooids involve a broad erasure of the methylation pattern since an important series of cytokines are demethylated, and immediately thereafter, a methylation of *novo* of the DNA takes place²⁰.

An incomplete reprogramming of the masculine germinal cells cause errors in the methylation that gives way to poor semen, associated with sub-fertility²¹. Semen with abnormal parameters or idiopathic male infertility presents numerous DNA sequences hypermethylated, in various specific

¹⁶ Schaefer, Ch..B., Ooi, S. K. T., Bestor, T.H., Bourchis, D. «Epigenetic Decisions in Mammalian Germ Cell» *Science* 316, 2007, 398-399.

¹⁷ Van der Auwera, I., D'Hooghe, T. «Super-ovulation of female mice delays embryonic and fetal development». 1237-1243.

¹⁸ Obata, Y., Hiura, H. «Epigenetically immature Oocytes lead to loss of imprinting during embryogenesis». *The Journal of Reproduction and Development* 57, 2011, 327-334.

¹⁹ Lopez-Moratalla, N., Palacios Ortega, S. «Retraso de la edad de la infertilidad y aumento del recurso a la reproducción asistida. Consecuencias en la salud de los hijos» *Cuadernos de Bioética*, 75, 2011, 259-272.

²⁰ Feil, R. «Epigenetic. Ready for the marks». *Nature* 461, 2009, 359-360.

²¹ Marques, C.J., Costa, P., Vaz, B., Carvalho, F., Fernandes, S., Barros, A., Sousa, M. «Abnormal methylation of imprinted genes in human sperm is associated with oligozoospermia». *Molecular Human Reproduction*. 14(2), 2008, 67-74; Marques, C.J., Carvalho, F., Sousa, M., Barros, A. «Genomic imprinting in disruptive spermatogenesis» *Lancet*. 363, 2004, 1700-1702; Hammoud, S.S., Purwar, J., Pflueger, C., Cairns, B.R., Carrell, D.T. «Alterations in sperm DNA methylation patterns at imprinted loci in two classes of infertility». *Fertility and Sterility* 94(5), 2010, 1728-1733; Poplinski, A., Tüttelmann, F., Kanber, D., Horsthemke, B., Gromoll, J. «Idiopathic male infertility is strongly associated with aberrant methylation of MEST and IGF2/H19 ICR1». *International Journal of Andrology* 33(4), 2010, 642-649.

genes, what suggests that the erasure of DNA methylation during epigenetic reprogramming is inadequate²². Apart from the DNA methylation, the importance of small-RNA²³ in the mature sperm has been seen. Some RNA molecules should be transported to the oocyte, persist in the zygote and are functionally important for the development of the embryo²⁴; well then, it has been found in sperm with low mobility alteration in these small-RNA.

It is important to highlight that the factor of male infertility is the most frequent cause to resort to ART, specifically to use the ICSI technique. To force in this way the fertilizing capacity of altered sperm involves consequences for the generated embryo.

3.3 Decline in fertility

In the last few years, a considerable decline of fertility in industrialized nation has been produced. On the other hand, feminine fertility is dependent on the age and there has been a delay in the age where women have their first child. On the other hand, male fertility that does not directly depend on age is being reduced, especially by the epimutations in the sperms produced by the environmental toxics. They are present in the environment in the form of herbicides, insecticides and fungicides to which they are daily exposed in many human populations.

The endocrine disruptors are a possible factor, possibly the most important, that contributes to the decline in fertility²⁵. It has an anti-androgen effect and diminishes the spermatogenesis, not because of changes in the DNA sequence but by inducing changes in the methylation pattern that regulates development genes and imprinting genes²⁶. These epimutations, that affect the methylation patterns, can be inherited through the germ-line, resulting in the intergenerational transmission of the inheritance of epigenetic states²⁷. At the same time, epimutations induced by hormonal disruptors are at the base of some tumors²⁸.

The number of males that suffer tumors at the reproductive age -leukemia, Hodgkin lymphomas and testicular tumors in germinal cells- has increased in the last twenty years and also those that survive cancer at an early age as the result of early detection and the improvement of the treatment protocols²⁹. So much the tumor itself as the treatment negatively influences in male fertility in the

²² Houshdaran, S., Cortessis, V.K., Siegmund, K., Yang, A., Laird, P.W., Sokol, R.Z. «Widespread epigenetic abnormalities suggest a broad DNA methylation erasure defect in abnormal human sperm». *PLoS One*. 2(12), 2007, e 1289.

²³ Burchis, D., Voinnet, O. «A small-RNA perspective on gametogenesis, fertilization, and early zygotic development. *Science* 330, 2010, 617-622.

²⁴ Krawetz, S.A. «Paternal contribution: new insights and future challenges». *Nature Review Genetics* 6, 2005, 633-642; Avendaño, C., Franchi, A., Jones, E., Oehninger, S. «Pregnancy-specific {beta}-1-glycoprotein 1 and human leukocyte antigen-E mRNA in human sperm: differential expression in fertile and infertile men and evidence of a possible functional role during early development». *Human Reproduction* 24, 2009, 270-277

²⁵ Anway, M.D., Cupp, A.S., Uzumcu, M., Skinner, M.K. «Epigenetic transgenerational actions of endocrine disruptors and male fertility». *Science* 308, 2005, 1466-1469; Guerrero-Bosagna, C.M., Skinner, M.K. «Epigenetic transgenerational effects of endocrine disruptors on male reproduction». *Seminars in Reproductive Medicine* 27, 2009, 403-408.

²⁶ Guerrero-Bosagna, C., Settles, M., Lucker, B.J., Skinner, M.K. «Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome». *PLoS ONE* 2010, 5, e13100.

²⁷ Allegrucci, C., Thurston, A., Lucas, E., Young, L.» Epigenetics and the germline». *Reproduction* 129, 2005, 137 - 149; Skinner, M.K., Manikkam, M., Guerrero-Bosagna, C. «Epigenetic transgenerational actions of endocrine disruptors» *Reproductive Toxicology* 31, 2011, 337-343.

²⁸ Birnbaum, L.S., Fenton, S.E. «Cancer and developmental exposure to endocrine disruptors». *Environ Health Perspect* 111, 2003, 389-394; Prins, G.S. «Endocrine disruptors and prostate cancer risk». *Endocrine-Related Cancer* 15, 2008, 649-656.

²⁹ Bray, F., Richiardi, L., Ekbom, A., Pukkala, E., Cuninkova, M., Møller, H. «Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. *International Journal of Cancer* 118, 2006, 3099-3111.

patient's future³⁰. In some malign tumors, especially in tumors of germ cells, the quality of the spermatozoids is already abnormal in the moment of diagnosis.

The cryopreservation of semen before cancer treatment is actually the only possible method to preserve fertility, subsequently needing ART, generally IVF, or ICSI³¹. The cryopreservation induces a certain deterioration of semen in good state, by which it is unknown if the risk for the offspring could be different for the children born after the same procedures in the population without cancer³², since the mechanism of natural selection does not exist in the implementation of ART. Therefore, it poses the obligation of a follow-up, in the long term, of these children.

Lastly, experiments with rats about differentiating or maturing *in vitro* the precursor cells of the spermatozoids, do not contribute any security at all for its possible posterior use to have offspring. It is the thought that the possibility of transplanting in the testicle precursor cells of the same patient gathered before his treatment, although it does not seem easy to assure lack of risks³³.

4. Problems of the techniques which are unsatisfactorily resolved

Multiple are the factors that intervene in the techniques, by which it resulted very difficult until recently to determine the cause of the lack of efficiency. On the other hand, the acquiring and quality of the oocytes obtained after the induction of ovarian stimulation, the process of the maturing of the same and the procurement and quality of the spermatozoids are important factors. It should be taken into account that for now it cannot be rectifying the possible anomalies of the gametes, by which that starting material for fertilization results problematic. On the other hand, the techniques of freezing-thawing of oocytes and embryos and their cultures *in vitro* strongly distance the embryo from the natural medium in its most vulnerable period of its life.

In fact, embryonic mortality –and perinatal- is very elevated and always greater than the one of the engendered in a natural way. The primordial biological situation is essential so much so for the early development of the embryo. Therefore, what refers to the maturity of the gametes in the body of the progenitors, the natural selection of the sperm in the feminine genital tract, maturation of the embryo in communication with the maternal Fallopian tubes as the mechanisms by which the nesting is prepared and the immunological tolerance of the mother towards the fetus³⁴.

Apart from the situation of the gametes, each one of these interactions is precise, attached, and delicate and that harms the initial and future development when they are detracted from the artificial procedures.

From some years ago, it is well known that the correct expression of the genes, throughout embryonic development and throughout its life, it is a process perfectly controlled by the epigenetic information that arises from the process itself and always in dependence of the medium.

³⁰ Sabanegh, E.S. Jr, Ragheb, A.M.» Male fertility after cancer» *Urology* 73, 2009, 225–231.

³¹ Dohle, G. R. «Male infertility in cancer patients: Review of the literature» *International Journal of Urology* 17, 2010, 327–331.

³² Grischenko, V.I., Dunaevskaya, A.V., Babenko, V.I. «Cryopreservation of human sperm using rapid cooling rates». *Cryo Letters* 24, 2003, 67–76.

³³ Geens, M., Goossens, E., De Block, G., *et al* “Autologous spermatogonial stem cell transplantation in man: current obstacles for a future clinical application” *Human Reproduction Update* 14, 2008, 121-130

³⁴ López Moratalla, N. «Fecundación *in vitro* y la pérdida en la relación intergametos y en la relación inicial madre-hijo». En: *La humanidad in vitro* (Coord. Jesús Ballesteros) Ed. Comares. Granada, 2000; Sánchez Abad, P.J., López-Moratalla, N. «Carencias de la comunicación biológica en las técnicas de reproducción asistida». *Cuadernos de Bioética* 70, 2009, 339-355.

4.1 Culturing medium of the embryo

The embryo in culture until the blastocyst stage, some five days after fertilization, it is very sensible to the environmental influences. The investigations conducted during the last decade have given way to significant improvements in the composition of the culturing medium. A first approach – “return to nature”³⁵ - consists in a sequential medium with embryo movement from one medium to another; these transfers add significant stress for the developing embryo and require intensive and costly work. A second focus – “leave the election of the embryo”³⁶ - that consists in a protocol of only a step shows advantages. Also a study that compares throughout various years both culturing systems, shows that the second focus, permits after the implantation of the blastocysts, a better development³⁷.

4.2 Freezing-thawing of embryos

To not carry out multiple embryo transfers and at the same time to not repeat the ovarian stimulation treatment, it became routine practice store in cold the embryos that are not transferred in the same cycle of stimulation.

The embryos are frozen in a culturing medium of tissues that also contain cryo-protectors and sugar and, in an alternative form, vitrification protocols are used in which the formation of ice crystals through the use of elevated concentrations of cryo-protectors and very high freezing speeds. Thawing occurs in the presence of adequate sugar concentrations not permeable with the aim of avoiding an over-hydration of the cells, at the same time that the dilution of the cryo-protector is produced.

Logically before proceeding to the transfer, the reanimation takes place –since the freezing of the embryonic life has been halted- in an *in vitro* culture of the thawed embryos during a period of 24 hours to assure that the development would continue.

In 1982, the birth of rats had been achieved from frozen embryos. The first intents of cryo-preservation of human embryos, followed by the transfer of embryos and births, took place later on. The implantation rates approximate to those obtained from embryos not frozen³⁸, however, the mortality with thawing is elevated³⁹, especially of those generated by ICSI. The injection, that permits the introduction of the spermatozoid into the interior of the ovum for its fertilization, possibly affects the membranes of the cells from the first divisions of the embryo.

The embryos generated by ICSI or by IVF, fresh or cryo-preserved present a series of anomalies - premature, low birth weight, delay in intrauterine growth, perinatal and infant mortality- of the same level. Now, the improvements of the cryo-preserved –greater birth weight and a lower

³⁵ Leese, H.J. «Human embryo culture: back to nature». *Journal of Assisted Reproduction and Genetics* 15, 1998, 466-468.

³⁶ Biggers, J.D. «Reflections on the culture of the preimplantation embryo». *The International Journal of Developmental Biology* 42, 1998, 879-884; Biggers, J.D., Racowsky, C. «The development of fertilized human ova to the blastocyst stage in KSOM (AA) medium: is a two-step protocol necessary?» *Reproductive Biomedicine Online* 5, 2002, 133-140.

³⁷ Keskinetepe, L. «Human Embryo Culture Dilemma Continues: «Back to Nature» or «Let the Embryo Choose» *Journal of Fertilization: In Vitro* 2, 2012,2. <http://dx.doi.org/10.4172/2165-7491.1000e112>.

³⁸ Kaufman, R.A., Menezo, Y., Hazout, A., Nicollet, B., DuMont, M., Servy, E.J. «Cocultured blastocyst cryopreservation: experience of more than 500 transfer cycles». *Fertility and Sterility* 64, 1995,1125-1129; [FIVNAT evaluation of frozen embryo transfers from 1987 to 1994] *Contraception, Fertilité, Sexualité* 14, 1996, 700-705.

³⁹ Testar, J., Lasalle, .B., Belaisch-Allart, J., Forman, R., Hazout, A., Volante, M., Frydman, R. “Human embryo viability related to freezing and thawing”. *American Journal of Obstetrics and Gynecology* 157, 1987,168-171; Pavone, M.E., Innes, J., Hirshfeld-Cryton, J., Kazar, R., Zhang, J. “Comparing thaw survival, implantation and live birth rates from cryopreserved zygotes, embryos and blastocysts”. *Journal of Human Reproduction Science* 4, 2011, 23-28.

percentage of premature births- on the fresh embryos, logically indicates that only those that withstand the process and do not die are transferred. Moreover, the maternal uterus is in better conditions for the embryo to implant because of temporary alienation, during the time of the conservation in cold, the conditions created by ovarian hyper-stimulation⁴⁰ in the maternal body.

According to the ESHRE records of the last years, the number of cycles for the generation of embryos at an international level fluctuates between 427,226 and 433,427 per year between 2009 and 2011⁴¹. The number of cycles with thawed embryos varies between 102,000 and 115,000. They come from donated ova 21,914 and 23,664 respectively. From them more than 5% in Europe and 10% in the USA and Canada cannot be transferred because they are defective. Of thawed embryos only around 10-15% achieve implanting, and of those, less than half reach term. To these losses, you have to add a percentage of prematurity and of mortality, similar to non-frozen born embryos.

The cryo-conservation of embryos, in the long term, only should be permitted to stable couples⁴² and with a commitment to transfer them at latter moments. Experience shows that with too much frequency they are not transferred, in that irrational consideration of “left-overs”.

4.3 Ova cryo-conservation

The cryo-conservation of the oocyte is considered a complement of *in vitro* fertilization⁴³ that permits its implementation to infertile women through donor programs. Initially, the cryo-conservation of oocytes was presented as a solution to preserve the fertility of women who undergo a sterilizing oncological treatment. Several studies show that it can protect the ovary before undergoing treatment⁴⁴ and preserving fertility with a posterior ovarian stimulation⁴⁵. On the other hand, and to not subject females to ART, positive steps have been taken to cryo-conserve ovarian tissue that later on is replanted⁴⁶ and can naturally conceive⁴⁷. It could be assumed then as an alternative to the freezing of embryos that causes so many losses.

This process has given way to a donation program and the conservation of ova, without medical

⁴⁰ Pelkonen, S., Koivunen, R., Gissler, M., Nuo- jua-Huttunen, S., Suikkari, A.M., Hyden-Granskog, C., Martikainen, H., Tiitinen, A., Hartikainen, A.L. «Perinatal outcome of children born after frozen and fresh embryo transfer: the Finnish cohort study 1995–2006». *Human Reproduction* 25, 2010, 914–923; Li, H.Z., Qiao, J., Chi, H.B., Chen, X.N., Liu, P., Ma, C.H. «Comparison of the major malformation rate of children conceived from cryopreserved embryos and fresh embryos». *Chinese Medical Journal* 123 (14), 2010, 1893-1897; De Mouzon, J., Goossens, V., Bhat- tacharya, S., Castilla, J.A., Ferraretti, A.P., Korsak, V., Kupka, M., Nygren, K.G., Nyboe Andersen, A.; European IVF-monitoring (EIM) Consortium, for the European Society of Human Reproduction and Embryology (ESHRE). «Assisted reproductive technology in Europe, 2006: results generated from European registers by ESHRE». *Human Reproduction* 25 (8), 2010, 1851-1862; Pinborg, A., Loft, A., Aaris Henningsen, A-K, Rasmussen, S., Nyboe Andersen, A. «Infant outcome of 957 singletons born after frozen embryo replacement: The Danish National Cohort Study 1995–2006». *Fertility and Sterility* 94, 2010, 1320–1327; Halliday, J. L., Ukoumunne, O.C., Baker, H.W.G., Breheny, S., Garrett, C., Healy, D., Amor D. «Increased risk of blastogenesis birth defects, arising in the first 4 weeks of pregnancy, after assisted reproductive technologies. *Human Reproduction* 25, 2010, 59–65.

⁴¹ International Committee for Monitoring Assisted Reproductive Technology, de Mouzon, J., Lancaster, P., Nygren, K.G., Sullivan, E., Zegers- Hochschild, F., Mansour, R., Ishihara, O., Adamson, D. «World collaborative report on Assisted Reproductive Technology, 2002». *Human Reproduction* 24 (9), 2009, 2310-2320; Nygren, K.G., Sullivan, E., Zegers-Hochschild, F., Mansour, R., Ishihara, O., Adamson, G.D., de Mouzon, J. «International Committee for Monitoring Assisted Reproductive Technology (ICMART) world report: assisted reproductive technology 2003». *Fertility and Sterility* 95, 2011, 2209 -2222.

⁴² Dondorp, W., de Wert, G. «Innovative reproductive technologies: risks and responsibilities». *Human Reproduction* 26, 2011, 1604–1608.

⁴³ Oktay, K., Cil, A.P., Bang, H. «Efficiency of oocyte cryopreservation: a meta-analysis. *Fertility and Sterility* 86, 2006, 70-80.

⁴⁴ Blumenfeld, Z., von Wolff, M., «GnRH- analogues and oral contraceptives for fertility preservation in women during chemotherapy. *Human Reprod Update* 14, 2008, 543-552; Beck-Fruchter, R., Weis, A., Shalev, E., «GnRh agonist therapy as ovarian protectants in female patient undergoing chemotherapy: a review of the clinical data». *Human Reproduction Update* 14, 2008, 553-561; Badawy, A., Elnashar, A., El-Ashry, M. «Gonadotropin-releasing hormone agonist for prevention of chemotherapy-induced ovarian damage: prospective randomized study». *Fertility and Sterility* 91, 2009, 694-697.

⁴⁵ Azim, A.A., Constantini-Ferrando, M., Oktay, K. «Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study». *Journal of Clinical Oncology* 26, 2008, 2630-2635.

⁴⁶ Oktay, K., Karlikaya, G. «Ovarian function after transplantation of frozen, banked autologous ovarian tissue» *New England Journal of Medicine* 342, 2000, 191.

⁴⁷ Oktay, K., Buyuk, E., Veeck, L. et al. «Embryo development after heterotopic transplantation of cryopreserved ovarian tissue. *Lancet* 363, 2004, 837-840.

reasons, for fertile women that wish to trespass the age limit of its natural fertility cycle. Thus, they could then store and conserve the ova and fertilize them later on if they desire it. It deals with –it is said- to overcome the “reproductive injustice” of maternity that conditions the professional and social interests of women⁴⁸. Moreover, it would solve –it is said- the demographic winter when it palliates the “involuntary” sterility of older women. It is not surprising then the standpoint that defends that there are “demographical reasons” to welcome the child born from women that are socially, economically, and physically capable of giving them a good start in life. Those born from another type of mothers, on the contrary, are not welcomed into the world?

The current situation of cryo-conservation is of great insecurity despite having progressed. It lacks the knowledge of structural and biochemical defects that involves its freezing due to the great size of the oocytes and the difficulty of the water movement and cryo-protectors through plasmatic membranes. In a similar manner of what occurred with the freezing of the embryos, the commercial interests made that the vitrification method be abandoned, already rehearsed⁴⁹, by the rather inefficient slow freezing⁵⁰.

Vitrification has improved in results and some data appears that shows that the vitrified oocytes show similar efficiency than the fresh ones in donation programs, in terms of pregnancy rate⁵¹; other data shows that a higher rate of malformations, in the short term, in the children born from vitrified ova fertilization than those coming from fresh ova⁵².

However, there is no data about the consequences in the long term of those born from the programs of the preservation of fertilization because of the maternal age. On the one hand, the data of the literature take to the conclusion that the rate of those born alive for each vitrified oocyte in women younger than 36 is of a 4-5%, this is, for each one born alive on average of some 20 to 15 vitrified oocytes is required.

This intent of solving with technique the question of delaying maternity further on than the natural limits requires a rational debate that is not taking place. Once again, only the high economic cost due to pregnancy, for each child born by these techniques⁵³, or even who should pay for such programs⁵⁴ is debated. In fact, the cost of the cycles in women with advanced age is superior⁵⁵.

The work group “ESHRE Task Force on Ethics and Law” changes the original message of 2004 that said that “freezing of oocytes for the preservation of fertility without medical indication should not

⁴⁸ Goold, I., Savulescu, J. «In favor of freezing eggs for non-medical reasons». *Bioethics* 23, 2009, 47–58; Homburg, R., Van der Veen, F., Silber, S.J. «Oocyte vitrification –women’s emancipation set in stone». *Fertility and Sterility* 91, 2009, 1319–1320.

⁴⁹ Chung, H.M., Hong, S.W., Lim, J.M., Lee, S.H., Won, M.D., Cha, T., Jung, M.T., Ko, J., Han, S.Y., Choi, D.H., Cha, K.Y. «In vitro blastocyst formation of human oocytes obtained from unstimulated and stimulated cycles after vitrification at various maturational stages». *Fertility and Sterility* 73, 2000, 545–551.

⁵⁰ Shirazi, A. “Mammalian Oocyte Cryo-preservation”. *Fertilization: In Vitro* 2, 2012, 2 <http://dx-doi-org/10-4172/2165-7491-1000e110>.

⁵¹ Cobo, A., Meseguer, M., Remohi, J., Pellicer, A. «Use of cryo-banked oocytes in an ovum donation programmer: a prospective, randomized, controlled, clinical trial». *Human Reproduction* 25, 2010, 2239–2246. Rienzi, L., Romano, S., Albricci, L., Maggiulli, R., Capalbo, A., Baroni, E., Colamaria, S., Sapienza, F., Ubaldi, F. «Embryo development of fresh ‘versus’ vitrified metaphase II oocytes after ICSI: a prospective randomized sibling-oocyte study». *Human Reproduction* 25, 2010, 66–73.

⁵² Noyes, N., Porcu, E., Borini, A. «Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies». *Reproductive Biomedicine Online* 18, 2009, 769–776; Wennerholm, U.B., Söderström-Anttila, V., Bergh, C., Aittomäki, K., Hazekamp, J., Nygren, K.G., Selbing, A., Loft, A. «Children born after cryopreservation of embryos or oocytes: a systematic review of outcome data». *Human Reproduction* 24, 2009, 2158–2172; Chian, R., Huang, J., Tan, S., Lucena, E., Saa, A., Rojas, A., Ruvalcaba Castellón, L.A., García Amador, M.I., Montoya Sarmiento, J.E. «Obstetric and perinatal outcome in 200 infants conceived from vitrified oocytes». *Reproductive BioMedicine Online* 16, 2008, 608–610.

⁵³ Connolly, M.P., Hoorens, S., Chambers, G.M., ESHRE Reproduction and Society Task Force. «The costs and consequences of assisted reproductive technology: an economic perspective». *Human Reproduction Update* 16, 2010, 603–613.

⁵⁴ Connolly, M.P., Hoorens, S., Chambers, G.M., ESHRE Reproduction and Society Task Force. «The costs and consequences of assisted reproductive technology: an economic perspective». *Human Reproduction Update* 16, 2010, 603–613.

⁵⁵ Griffiths, A., Dyer, S.M., Lord, S.J., Pardy, C., Fraser, I.S., Eckermann, S. «A cost-effectiveness analysis of in-vitro fertilization by maternal age and number of treatment attempts». *Human Reproduction* 25, 2010, 924–931.

encouraged". However, on the other hand, it approves it although it recognizes that there are still more possibilities that a woman has a healthy child through natural reproduction at a relatively young age⁵⁶.

Once again, it imposes the "medicalization" system of the personal or social problems, paradigm of the tendency to find medical answers to human and social problems. The long-term consequences for future generations were not looked at, but by investigating the results on the use of the techniques in a retrospective manner.

Information is essential. These options do not have a guarantee of success. The best option is to find solutions so that maternity takes place in the period of the natural feminine fertility cycle at least until they are certain that the technique is able to modify with success the natural feminine fertility cycle.

5. Health of the women submitted to ART

Several studies show that pregnancies after IVF have more complications for the mother as well as for those born, if they are compared with natural gestations⁵⁷.

5.1 Multiple pregnancies

A continued international recommendation exists of avoiding multiple pregnancies, reducing ovarian stimulation and transferring one sole embryo, since prematurity and low birth weight that they have, is the main cause of the malformations and adverse characteristics⁵⁸. According to demographic records of the last twenty years, the rate of twin labor has doubled, of triplets it has increased by six-fold due to the IVF by the transfer of more than one simultaneous embryo⁵⁹. The task of proposing and achieving the transfer of a sole embryo is in the hands of the professionals⁶⁰. Several studies show that sole gestated have less of a risk of alterations than twins or triplets⁶¹. However, couples that resort to ART prefer it to be twins instead of singletons⁶².

5.2 Psychological factors of the pregnancies

⁵⁶ ESHRE Task Force on Ethics and Law. «Taskforce 7: ethical considerations for the cryo-preservation of gametes and reproductive tissues for self-use». *Human Reproduction* 19, 2004, 460–462; ESHRE Task Force on Ethics and Law, Dondorp, W., de Wert, G., Pennings, G., Shenfield, F., Devroey, P., Tarlatzis, B., Barri, P., Diedrich, K. «Oocyte cryo-preservation for age-related fertility loss». *Human Reproduction* 27 (5), 2012, 1231–1237.

⁵⁷ Källén, B. «Maternal morbidity and mortality in in-vitro fertilization». *Best Practice & Research Clinical Obstetrics and Gynaecology* 22, 2008, 549–558; Venn, A., Hemminki, E., Watson, L. *et al.* «Mortality in a cohort of IVF patients» *Human Reproduction* 16, 2001, 2691–2696.

⁵⁸ Yoon, G., Beischel, L.S., Johnson, J.P., Jones, M.C. «Dizygotic twin pregnancy conceived with assisted reproductive technology associated with chromosomal anomaly, imprinting disorder, and monochorionic placentation». *Journal of Pediatrics* 146, 2005, 565–567. Tang, Y., Ma, C.X., Cui, W., Chang, V., Ariet, M., Morse, S.B., Resnick, M.B., Roth, J. «The risk of birth defects in multiple births: a population-based study» *Maternal and Child Health Journal* 10, 2006, 75–81; Li, S.J., Ford, N., Meister, K., Bodurtha, J. «Increased risk of birth defects among children from multiple births» *Birth Defects Research A Clinical and Molecular Teratology* 67, 2003, 879–885; Allen, C., Bowdin, S., Harrison, R., Sutcliffe, F., Brueton, A.G., Kirby, L., Kirkman-Brown, G., Barrett, J., Reardon, C., Maher W. «Pregnancy and perinatal outcomes after assisted reproduction: a comparative study». *Irish Journal of Medical Science* 177, 2008, 233–241.

⁵⁹ Barri, P.B., Buenaventura, C., Clua, E. «Transferencia selectiva de un único embrión como prevención del embarazo múltiple» *Anales de la Real Academia Nacional de Farmacia* 76(4), 2010, 531–540.

⁶⁰ Barri, P.B. «Multiple pregnancies: a plea for informed caution». *Human Reproduction Update* 11, 2005, 1–2.

⁶¹ Jackson, R.A., Gibson, K.A., Wu, Y.W., Croughan, M.S. «Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis». *Obstetrics and Gynecology* 103, 2004, 551–563; Helmerhorst, F.M., Perquin, D.A., Donker, D., Keirse, M.J. «Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies». *BMJ* 328, 2004, 261; O'Brien, F., Roth, S., Stewart, A., Rifkin, L., Rushe, T., Wyatt, J. «The neurodevelopmental progress of infants less than 33 weeks into adolescence». *Archives on Disease Childhood* 89, 2004, 207–211; Saigal, S., den Ouden, L., Wolke, D., Hoult, L., Paneth, N., Streiner, D.L., Whitaker, A., Pinto-Martin, J. «School-age outcomes in children who were extremely low birth weight from four international population based cohorts». *Pediatrics* 112, 2003, 943–950.

⁶² Ryan, G.L., Zhang, S.H., Dokras, A., Syrop, C.H., Van Voorhis, B.J. «The desire of infertile patients for multiple births». *Fertility and Sterility* 81, 2004, 500–504; Child, T.J., Henderson, A.M., Tan, S.L. «The desire for multiple pregnancy in male and female infertility patients». *Human Reproduction* 19, 2004, 558–561.

The emotional impact for the progenitors is usually more intense than in natural procreation. Depressive and anxiety states of women who have undergone ICSI or IVF have been analyzed. The analysis shows that they are higher at the beginning of the process in comparison with those that tried natural conception and that this difference persisted in time⁶³. A longitudinal study was carried out to know what happens with twin pregnancies⁶⁴. For all progenitors, in general, the symptoms for depression are always greater than when the pregnancy is of only one. But, the parents of twins generated by ART in comparison with the parents of twins conceived naturally are more resistant to stress factors related with the possible lack of health of the children, which is probably due to the positive attitude and preparation ante the twin pregnancy.

5.3 Ovarian stimulation

Infertility treatments –FIVET, ICSI or insemination- require a prior ovarian stimulation with the end of obtaining more ova and/or that these mature. The use of drug inductors of ovulation to stimulate the production of ovarian follicles is very widespread as independent therapy and also inside the *in vitro* fertilization cycles. The compound inductors of ovulation used are clomiphene citrate that has been used since the decade of the sixties and is still considered the best treatment for women with anovulatory infertility, the human chorionic gonadotrophin⁶⁵ (hCG), or the follicle stimulating hormone (FSH). It has not been obtained from these stimulants results in ovarian rejuvenation before natural aging by the women's age.

It is well known that ovarian stimulation treatment has risks⁶⁶. Ovarian hyper-stimulation syndrome is a complication due to an excessive response of the ovaries after the administration of exogenous gonadotrophins FSH or hCG⁶⁷. As a consequence, in its severe forms, diverse symptoms can appear, such as the increase in ovarian size along with the development of cysts, the acute extravasation of fluids outside the bloodstream (ascites, pleural or pericardium effusion), hydro-electrolyte disorders, kidney failure, respiratory difficulty and episodes of thromboembolism⁶⁸.

Apart from ovarian torsion⁶⁹, the risk of pre-eclampsia increased with the doses of ovarian stimulation that indicates an association with a decline of the ovarian reserve⁷⁰. Some effects – increase risk of placenta previa, placental abruption, and hemorrhages- seem to be because this stimulation affects the implantation of the embryo after the transfer to the uterus, since the function of the endometrium around the moment of implantation⁷¹ is fundamental.

⁶³ Vahratian, A., Smith, Y.R., Dorman, M., Flynn, H.A. «Longitudinal depressive symptoms and state anxiety among women using assisted reproductive technology». *Fertility and Sterility* 95, 2011, 1192-1194.

⁶⁴ Vilska, S., Unkila-Kallio, L., Punamaki, R.L., Poikkeus, P., Repokari, L., Sinkkonen, J., Tiitinen, A., Tulppala, M. «Mental health of mothers and fathers of twins conceived via assisted reproduction treatment: a 1-year prospective study». *Human Reproduction* 24, 2009, 367-377.

⁶⁵ Melo, M., Bellver, J., Garrido, N., Meseguer, M., Pellicer, A., Remoh, J. "A prospective, randomized, controlled trial comparing three different gonadotropin regimens in oocyte donors: ovarian response, in vitro fertilization outcome, and analysis of cost minimization". *Fertility and Sterility* 94, 2010, 958-964.

⁶⁶ Källén B. «Maternal morbidity and mortality in in-vitro fertilization». *Best Practice & Research Clinical Obstetrics and Gynaecology* 22, 2008, 549-558

⁶⁷ Delvigne, A., Rozenberg, S. «Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review». *Human Reproduction Update* 8, 2002, 559-577.

⁶⁸ De Leener, A., Montanelli, L., Van Durme, J., Chae, H., Smits, G., Vassart, G., *et al.* «Presence and absence of follicle-stimulating hormone receptor mutations provide some insights into spontaneous ovarian hyperstimulation syndrome physiopathology». *Journal of Clinical Endocrinology and Metabolism* 91, 2006, 555-562; Källén, B., Finnström, O., Nygren, K.G. *et al.* «In vitro fertilization in Sweden: obstetric characteristics, maternal morbidity and mortality». *BJOG* 112, 2005, 1529-1535; Klemetti, R., Sevón, T., Gissler, M. *et al.* «Complications of IVF and ovulation induction». *Human Reproduction* 20, 2005, 3293-3300.

⁶⁹ Gorkemli, A., Camus, M., Clasen, K. «Adnexal torsion after gonadotrophin ovulation induction for IVF or ICSI and its conservative treatment». *Archives of Gynecology and Obstetrics* 267, 2002, 4-6.

⁷⁰ Woldringh, G.H., Frunt, M.H., Kremer, J.A. *et al.* «Decreased ovarian reserve relates to pre-eclampsia in IVF/ICSI pregnancies». *Human Reproduction* 21, 2006, 2928-2954.

⁷¹ Healy, D.L., Breheny, S., Halliday, J., Jaques, A., Rushford, D., Garrett, C., Talbot, J.M., Baker, H.W.G. «Prevalence and risk factors for obstetric hemorrhage in 6730 singleton births after assisted reproductive technology in Victoria Australia». *Human Reproduction* 25, 2010,

On the other hand, ovarian hyper-stimulation syndrome increases the risks of involuntary miscarriages⁷², the loss of one of the two twins⁷³ and premature births⁷⁴.

It has also been analyzed the possible association between the treatments of ovarian induction and the development of tumors although the data is not thorough due to the employment of different doses and of the time that the administration has prolonged itself. Even so, there are papers that cast data that should be taken into account.

The administration during more than 12 months increases two times more the risk of developing cancer than those that finish the treatment in less than a year⁷⁵; other studies indicated a greater risk of suffering uterine cancer, ovarian, breast, malignant melanoma, and non-Hodgkin lymphoma⁷⁶.

It has been published, with a limited sample, a study⁷⁷ that shows that donors with a good response to ovarian stimulation can reduce the doses of gonadotrophin bettering the fertilization rate and the quality of the embryo. In 2012⁷⁸, it was observed that in high risk women with the Syndrome their ovary could be stimulated with one sole doses low in analogues of the gonadotrophin.

Some of the women diagnosed with one of these problems resort to IVF with the donation of ova on behalf of young females. Obviously, thorough information is necessary for the young oocyte donors, as has been demonstrated in prospective studies⁷⁹ of donors between 15 to 18 years, there exists minor complications in the procedures (8.5%) and serious (0.7%) and 9% of the donors had to interrupt the ovarian stimulation after having initiated it.

Considering this Syndrome as the most serious of the ART complications⁸⁰, parameters are not achieved that can predict the risk⁸¹.

265–274. Romundstad, L.B., Romunstad, P.R., Sunde, A. *et al.* «Increased risk of placenta previa in pregnancies following IVF/ ICSI; a comparison of ART and non-ART pregnancies in the same mother» *Human Reproduction* 21, 2006, 2353–2358.

⁷² Razieli, A., Friedler, S., Schachter, M. *et al.* «Increased early pregnancy loss in IVF patients with severe ovarian hyperstimulation syndrome» *Human Reproduction* 17, 2002, 107–110.

⁷³ Wang, J.X., Norman, R.J., Wilcox, A.J. «Incidence of spontaneous abortion among pregnancies produced by assisted reproductive technology». *Human Reproduction* 19, 2004, 272–277; De Sutter, P., Bontinck, J., Schutyser, V. *et al.* «First-trimester bleeding and pregnancy outcome after assisted reproduction» *Human Reproduction* 21, 2006, 1907–1911.

⁷⁴ Tan, S.L., Doyle, P., Campbell, S. *et al.* «Obstetric outcome of in vitro fertilization pregnancies compared with normally conceived pregnancies» *American Journal of Obstetrics and Gynaecology* 167, 1992, 778–784; Ochsenkühn, R., Strowitzki, T., Gurtner, M. *et al.* «Pregnancy complications, obstetrics risks, and neonatal outcome in singleton and twin pregnancies after GIFT and IVF» *Archives of Gynaecology and Obstetrics* 268, 2003, 256–261.

⁷⁵ Calderon Margalit, R., Friedlander, Y., Yanetz, R., Kleinhaus, K., Perrin, M.C., Manor, O., *et al.* «Cancer risk after exposure to treatments for ovulation induction». *American Journal of Epidemiology* 169(3), 2009, 365–375.

⁷⁶ Althuis, M., Moghissi, K., Westhoff, C., Scoccia, B., Lamb, E., Lubin, J., *et al.* «Uterine cancer after use of clomiphene citrate to induce ovulation». *American Journal of Epidemiology* 161, 2005, 607–615; Brinton, L., Lamb, E., Moghissi, K., Scoccia, B., Althuis, M., Mabie, J., *et al.* «Ovarian cancer risk after the use of ovulation-stimulating drugs». *Obstetrics and Gynecology* 103(6), 2004, 1194–1203; Modan, B., Ron, E., Lerner Geva, L., Blumstein, T., Menczer, J., Rabinovici, J., *et al.* «Cancer incidence in a cohort of infertile women» *American Journal of Epidemiology* 147, 1998, 1038–1042; Doyle, P., Maconochie, N., Beral, V., Swerdlow, A., Tan, S.L. «Cancer incidence following treatment for infertility at a clinic in the UK». *Human Reproduction* 17, 2002, 2209–2213; Kashyap, S., Moher, D., Fung, M.F.K. *et al.* «Assisted reproductive technology and the incidence of ovarian cancer: A meta-analysis». *Obstetrics and Gynecology* 103, 2004, 785–794.

Kristiansson, P., Bjor, O., Wramsby, H. «Tumour incidence in Swedish women who gave birth following IVF treatment». *Human Reproduction* 22, 2007, 421–426; Hannibal, C.G., Jensen, A., Sharif, H., *et al.* «Malignant melanoma risk after exposure to fertility drugs results from a large Danish cohort study». *Cancer Causes Control* 19, 2008, 759–765.

⁷⁷ Rubio, C., Mercader, A., Alama, P., Lizan, C., Rodrigo, L., Labarta, E., Melo M., Pellicer, A., Remohí, J. «Prospective cohort study in high responder oocyte donors using two hormonal stimulation protocols: impact on embryo aneuploidy and development». *Human Reproduction* 25, 2010, 2290–2297.

⁷⁸ Maselli, A., Wilding, M., del Grande, S., Riccio, S., Di Matteo, L., Dale, B. «Controlled ovarian hyperstimulation through gonadotrophin releasing hormone agonist for patients at risk of hyperstimulation syndrome». *Journal of Fertilization In Vitro* 2, 2012, 1. <http://dx.doi.org/10.4172/2165-7491.1000103>

⁷⁹ Maxwell, K.N., Cholst, I.N., Rosenwaks, Z. «The incidence of both serious and minor complications in young women undergoing oocyte donation» *Fertility and Sterility* 90, 2008, 2165–2171.

⁸⁰ Shahin AY. «The problem of IVF cost in developing countries: has natural cycle IVF a place?» *Reproductive Biomedicine Online* 15, 2007, 51.

⁸¹ Bellver, J., Ferrando, M., Garrido, N., Pellicer, A. «Blood group and ovarian hyperstimulation syndrome» *Fertility and Sterility* 93, 2010, 270–271.

Finally, obstetric hemorrhages are even more frequent in singleton births after *in vitro* fertilization, ICSI and GIFT⁸².

6. Problems in family relationships

It is well known that paternal-filial relationships, family/familiars, are profoundly human and necessary for the person. This is a perception that is shared by those who profess the most diverse creeds and very different ideological convictions. At the same time it is evident, at the very least, the use of the gametes from donors different from the gestating mother and the legal parents or the detention of the cryo-conserved embryo's life, etc., entails a warning of the dissolution of natural family relationships⁸³.

Psychological disorders have been described with negative impact so much so in children as in their families⁸⁴. The couple presents psychological impact during the treatment that extends in time, whether the result has been successful or has failed.

Regarding children there is no conclusive data. On the one hand, it has been described that they do not offer significant statistical differences in what refers to the functional and psychosocial development in comparison with children conceived in a natural way. Some studies that have investigated neuromotor, cognitive, language and conduct development contribute reassuring data on the psychological function, without any evidence of the specific risks for neurodevelopment disorders or language development⁸⁵. The children of multiple pregnancies showed a delay in some aspects of language development and in contrast, described a tendency to emotional symptoms⁸⁶.

6.1 Gamete donation and the right of the child to know the identity of their progenitors

Little investigation exists about how legal parents deal with the nature of conception of their children by donors or the single mother that chooses for her child the single parent family model to which these ART gives access.

In some countries -the United Kingdom- there exist the legal right to receive information about their father and more recently to know who their paternal siblings are. In contrast, in other countries, as in Israel, have a policy of secrecy and anonymity and only permit that some information be given that does not identify the person.

⁸² Healy, D.L., Breheny, S., Halliday, J., Jaques, A., Rushford, D., Garrett, C., Talbot, J.M., Baker, H.W.G. «Prevalence and risk factors for obstetric haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria Australia». *Human Reproduction* 25, 2010, 265–274.

⁸³ Olivennes, F., Ramogidas, S., Golombok, S. «Children's cognitive development and family functioning in a large population of IVF/ICSI twins». *Fertility and Sterility* 82, 2004, S37-S37; Ponjaert-Kristoffersen, I., Tjus, T., Nekkebroeck, J., Squires, J., Verte, D., Heimann, M. *et al.* «Psychological follow-up study of 5-year-old ICSI children». *Human Reproduction* 19, 2004, 2791-2797; Barnes, J., Sutcliffe, A.G., Kristoffersen, I., Loft, A., Wennerholm, U., Tarlatzis, B.C., *et al.* «The influence of assisted reproduction on family functioning and children's socio-emotional development: results from a European study». *Human Reproduction* 19, 2004, 1480-1487.

⁸⁴ Verhaak, C.M., Smeenk, J.M., Evers, A., Kremer, J.A., Kraaimaat, F.W., Braat, D.D. «Women's emotional adjustment to IVF: a systematic review of 25 years of research». *Human Reproduction Update* 13, 2007, 27.

⁸⁵ Wagenaar, K., Huisman, J., Cohen-Kettenis, P.T., Delemarre-van de Waal, H.A. «An overview of studies on early development, cognition, and psychosocial wellbeing in children born after *in vitro* fertilization». *Journal of Developmental and Behavioral Pediatrics* 29, 2008, 219–30; Leunens, L., Celestin-Westreich, S., Bonduelle, M., Liebaers, I., Ponjaert-Kristoffersen, I. «Follow-up of cognitive and motor development of 10-year-old singleton children born after ICSI compared with spontaneously conceived children». *Human Reproduction* 23, 2008, 105–111; Nekkebroeck, J., Bonduelle, M., Desmyttere, S., Van den Broeck, W., Ponjaert-Izat, Y., Goldbeck, L. «The development of children from assisted reproduction—a review of the literature». *Praxis der Kinderpsychologie und Kinderpsychiatrie* 57, 2008, 264–281.

⁸⁶ Freeman, T., Golombok, S., Olivennes, F., Ramogida, C., Rust, J. «Psychological assessment of mothers and their assisted reproduction triplets at age 3 years» *Reproductive Biomedicine Online* 15, 2007, 13–17.

It begins to be frequent⁸⁷, on the other hand, that many progenitors search for, through the Official Registry, those that were the gamete donors for their child's conception, and their possible siblings, with the ends of facilitating contact between families that share the same biological father. This is especially so in the case of single parent families where they look for creating a family feeling and a greater security for their child's sense of identity by knowing their siblings.

There is a growing opinion that those born by assisted reproduction should be informed of their conception by gamete donation⁸⁸, given the importance that is currently given to genetics because it determines diverse characteristics. Other reasons would also be the possible transmission of unknown genetic diseases, and, potentially the possibility of incest by a relationship between a brother and a sister not aware of their genetic connection. The negation of the knowledge of one of the genetic parents can have psychological consequences for the offspring who can feel deprived of the information that they need to develop a broad sense of identity⁸⁹.

However, very few parents talk to their children about their conception by donor⁹⁰. There are various reasons not to reveal that fact. On the one hand, the desire to protect the children from the anguish of not being able to obtain any information on their biological father and, on the other, of wanting to protect them from the child's potential rejection, or of the social stigma associated with male infertility⁹¹. No obstante, the secret seems to be prejudicial for them so much physically as psychosocially⁹², and has a negative impact on the internal dynamics of the family⁹³.

Few studies have focused on single-mother families with a child conceived by sperm donation and that have to explain the absence of a father. Sixty-two single mothers who had conceived by donors were asked in a survey⁹⁴ if: a) if they would like to know the identity of their donor; b) if they would like to give their child the opportunity of knowing their father's identity at the age of eighteen; c) if they had the intention of doing so in the future, and; d) if they were worried about this topic.

Half of those surveyed wanted to know the identity of the sperm donor for themselves, in order to knowing what characteristics their child had from their biological father; to thank him for letting her be a mother, even to talk to him about the child and that he could thus have an image of him. Less than 20% of the mothers clearly expressed that they did not want their children to have access to the donor's identity at the age of eighteen. The remaining 80% were divided between the clear support to that possibility and those that had mixed feelings in that regard.

Around two thirds of the mothers had not revealed the conception by donors to their children, but

⁸⁷Freeman, T., Jadva, V., Kramer, W., Golombok, S. «Gamete donation: parents' experiences of searching for their child's donor siblings and donor». *Human Reproduction* 34, 2009, 505–516; Scheib, J.E., Ruby, A. «Contact among families who share the same sperm donor *Fertility and Sterility* 90, 2008, 33–34; Scheib, J.E., Riordan, M., Rubin, S. «Adolescents with open identity sperm donors: reports from 12–17 years old». *Human Reproduction* 20, 2005, 239–252.

⁸⁸Greenfeld, D.A. «The impact of disclosure on donor gamete participants: donors, intended parents and offspring». *Current Opinion in Obstetrics and Gynecology* 20, 2008, 265–268.

⁸⁹Baran, A., Pannor, R. *Lethal Services: the Psychology of Donor Insemination, Problem and Solution*. Cambridge: Armstead Press, Seven Hills, NSW, 1993.

⁹⁰Burr, J., Reynolds, P. «Thinking ethically about genetic inheritance: liberal rights, communitarianism and the right to privacy for parents of donor insemination children». *Journal of Medical Ethics* 34, 2008, 281–284. Jadva, V., Freeman, T., Kramer, W., Golombok, S. «The experiences of adolescents and adults conceived by sperm donation: comparisons by age of disclosure and family type». *Human Reproduction* 24, 2009, 1909–1919.

⁹¹Snowden, R., Mitchell, G.D., Snowden, E.M. *Artificial Reproduction: A Social Investigation*. George Allen & Unwin, London, 1983.

⁹²Landau, R. «The management of genetic origins: secrecy and openness in donor assisted conception in Israel and elsewhere». *Human Reproduction* 13, 1998, 3268–3273

⁹³Paul, M.S., Berger, R. «Topic avoidance and family functioning in families conceived with donor insemination». *Human Reproduction* 22, 2007, 2566–2571.

⁹⁴Paul, M.S., Berger, R. «Topic avoidance and family functioning in families conceived with donor insemination». *Human Reproduction* 22, 2007, 2566–2571.

had the intention of doing so in the future. A total of 77.4% of the mothers reported that they were worried about the donors of conception since they thought their children would need it for their psychosocial development, particularly during adolescence. This was because of fear that genetic disorders would appear and of not having access to genetic information when it would be necessary. Another reason was because they also feared the possibility of marriage amongst siblings.

6.2. *Maternity by substitution*

The possibility of recurring to maternity by surrogacy arose in the framework of ART, for women that suffered a uterine pathology. To lend the womb to gestate the child of a woman with this type of problem initially was seen as an altruist gift. Later on, it began to recognize and justify that it should have tied to it an economic benefit. In a third stage, this gestational service has passed on to be a new form of feminine slavery.

Surrogate motherhood is legally prohibited in Spain –article 10 of the law 14/2006 avoiding in this manner the conflict that is created when the mother that gestates decides to keep the baby. In said case, whatever contract by which she would renounce to the maternal filiation in favor of the contracting party or of a third party would lack validity. Maternity is determined by birth; mother is who gives birth and not who has paid for the gestation. Only the biological father could initiate a possible claim of liability in the case of having been inseminated with his gametes.

Hence, during pregnancy such a community of life so profound and intimate has been created that the brain of the gestating woman is converted into a maternal brain. A bond of emotional closeness and affection of such force is generated that it leads her to feel as a mother.

The uterine mother is condemned to living those months of her life from a mere functional perspective, with indifference and with the aim of abandoning it and not as an event that fully concerns her. In fact, more than 10% of uterine mothers need therapy to overcome the acquired obligation of handing it over when it is born⁹⁵.

On the other hand, as the experts from the National Ethics Committee of France point out in 2010 no one could foresee the consequences of a process like this in the psyche of the offspring, that one day will know that he was the object of a contract⁹⁶.

6.3 *Maternity shared by two women*

Presented for the first time in Spain, in the Institute CEFER of Reproduction, with the pretension of a new family model constituted by two biological lesbian mothers, one that contributed the ova and the other that goes through the gestation, and that have been denominated ROPA model (Reception of oocytes from partner)⁹⁷. Fourteen lesbian couples underwent a treatment through the ROPA technique. Six pregnancies were obtained from thirteen embryonic transfers. There were two involuntary miscarriages followed by three pregnancies, one of them of twins. One healthy girl was born.

This was the first time that it is published in a scientific medical magazine, although beforehand the possibility of sharing maternity between two women –family model “mother egg, mother womb”- had been commented in means of communication upon knowing that some couple had been

⁹⁵ Wilkinson, S. «The exploitation argument against commercial surrogacy» *Bioethics* 17, 2003, 180-186; Hanna, J.K. «Revisiting child-based objections to commercial surrogacy» *Bioethics* 24, 2010, 341-347.

⁹⁶ Parks, J. «Care ethics and the global practice of commercial surrogacy» *Bioethics* 24, 2010, 333-339.

⁹⁷ Marina, S., Marina, D., Marina, F., Fosas, N., Galiana, N., Jové, I. «Sharing motherhood: biological lesbian co-mothers, a new IVF indication». *Human Reproduction* 25, 2010, 938-941.

successful⁹⁸.

From the technical point of view ROPA does not differ from an oocyte donor process that fertilized by sperm are transferred to the uterus of a woman different from the donor. However, from a human point of view profoundly differ: both women desire to experiment and participate in the start of a life, of a family. It is obviously only legal in countries like Spain, from 2005, the rights of homosexual couples, including the reproductive, were equaled with those of heterosexual couples (Law 13/2005).

Since more than 30 years some women without a male couple has accomplished offspring by insemination by donor, generally from semen banks. Lesbian women in Spain have always had legal access to the use of sperm donors (Law 35/1988 article 5.5, of 22 of November of 1988; Law 14/2006 article 5.5, of 26 of May of 2006). Yet, the insemination of both by semen from the same male does not imply the same satisfaction than this shared maternity. Initially, the child generated by insemination of one of the females was considered as being an adoption by the other. With the ROPA system, they claim, "if women are fertile they can interchange their embryos; in other words, a woman can gestate the embryos created with the ova of their couple, and vice versa. This would be the highest level of participation in the couple's reproduction".

Unlike the single woman inseminated that assumes the responsibility of raising the children on her own, the lesbians wish to share the maternal experience, instead of having the couple as a mere spectator.

For the promoters - cfr. Marina- the ROPA technique meets the requisites of the three ethical principles of medicine: 1) do good to the couple that wishes it and the child, that can be loved , cared for and educated, since bringing a child into the world is to do something positive for him. 2) Not harm or do wrong, since as per they assert "the development of the child does not seem to be affected to live in a family with two mothers, because of the absence of a father, or because of the maternal homosexuality, that does not affect the development of the child's sexual identity. 3) They are informed in a manner that the autonomy of the couple is respected and the authority to make decisions.

Another question would be, as they claim, if it is medically acceptable for fertile people since all FIVET has a risk, is complex and costly. The response is left in the hands of the doctor if the law does not specify that ROPA be only for lesbians in case that they be infertile.

A commentary has been published of this paper⁹⁹ that includes a discussion of another published 15 years ago about a case then still hypothetical of ROPA, after a debate in the USA on Ethics and Conduct¹⁰⁰. In that anterior publication McCormick affirmed that the principle of charities, according to which the notion of the doctors called to "do good" is not unconditional, since its profession contributes a clear orientation of fighting the illness and helping the patients.

As is logical it is posed that according to the principle of non-maleficence would carry out an insemination before subjecting women to the risks of IVF treatment. Once again, the supporters of ROPA turn to the patient's autonomy to choose insemination or ROPA, if they are well informed and accept willingly the risks. The contrary would be paternalism. Moreover, they do not only want

⁹⁸ Ehrensaft, D. «Just Molly and me, and do- nor makes three: Lesbian motherhood in the age of assisted reproductive technology». *Journal of Lesbian Studies* 12, 2008, 161–178; Pelka, S. «Sharing mother- hood: maternal jealousy among lesbian co-mothers». *Journal of Homosexuality* 56, 2009, 195–217.

⁹⁹ Dondorp, W.J., De Wert, G.M., Janssens, P.M.W. «Shared lesbian motherhood: a challenge of established concepts and frameworks». *Human Reproduction* 25, 2010, 812–814.

¹⁰⁰ Chan, C.S., Fox, J.H., McCormick, R.A., Murphy, T.F. «Lesbian motherhood and genetic choices». *Ethics and Behavior* 3(2), 1993, 211–222.

to be helped to have a child, but they want a child for who they will both be biological mothers: one by her genes and the other by the gestation of the child.

However, ROPA defenders claim that, even in the case of there being a sterility problem in one of the two women, that is to say implemented in healthy women it should be considered as good medical practice. They affirm, in fact, the limits of the profession have progressively been lost, and the concepts of “health” and “illness” are not as clear and objective as suggests the argument of medical art. ART should be understood more as a treatment for *voluntary sterility* than as an intervention destined to correct a biological defect: the good and the bad of health are not only a question of biological facts, but a question of social conventions. In the domain of ART one has to rely on the social comprehension of the significance and the bravery that having children can bring to human life and to homosexual relationships.

Although being a biological mother is not the same as being a uterine mother, little is known of how the election of ROPA facilitates the dynamic familiar unlike insemination. Pelka¹⁰¹ addresses this question and concludes that to know oneself as genetic mother or uterine “seems to better the emotional insecurities in the homes of double mother, so much so in the external (in response to the dares of the legitimacy derived from maternity) as internally (when it confronts to the infantile preference for the other)”.

It is argued, and only slightly, against ROPA against insemination, that this last option is of a lower economical cost and does not imply the creation of remaining embryos. Once again, the lesser cost-effectiveness appears as “the argument” convincing as far as shared maternity, up until now carried out in the private sphere will pass to the public centers. In the same manner that it is of justice to understand this debate in the context of the increasing social acceptance of homosexuality that has given in various countries the legalization of marriages for homosexual couples, also has to have a distributive justice referred to the just distribution of the scarce public means.

In all of this discussion, it is forgotten that in whatever case they require a third that contributes sperm and is the biological father of that child. They, as single mothers and differently from heterosexual couples, have to explain the absence of a father for their children; thus, they are more apt to reveal the information about the conception¹⁰² and their children of knowing the identity of their father.

7. Legal questions in ART matters

In some countries, mainly Italy, the legislation- Italian law 40/2004- considers artificial fertilization as a recourse permitted in the case that other efficient therapeutic methods do not exist to eliminate the causes of infertility or sterility, that medically assisted procreation is not a natural procreative alternative method but it is the last therapeutic resort against sterility. It only permits homologous fertilization by which legal paternity conforms to the biological.

On the contrary, in Spain –Law 14/2006- refers to the donors, to the contract of donation and the legal determination of the filiation that artificial reproduction assumes in regards with the offspring born by these technique so much so for the husband as for the unmarried male. In other words, to

¹⁰¹ Pelka, S. «Sharing motherhood: maternal jealousy among lesbian co-mothers». *Journal of Homosexuality* 56, 2009, 195–217.

¹⁰² Brewaeys, A. «Review: parent-child relationships and child development in donor insemination families». *Human Reproduction Update* 7, 2001, 38–46; Brewaeys, A., Ponjart-Kristoffersen, I., Van Steirthegehem, A.C., Devroey, P. «Children from anonymous donors- an inquiry into homosexual and heterosexual parent attitudes». *Journal of Psychosomatic Obstetrics and Gynaecology* 14, 1993, 23–25; Vanfraussen, K., Ponjart-Kristoffersen, I., Brewaeys, A. «Why do children want to know more about the donor? The experience of youngsters raised in lesbian families». *Journal of Psychosomatic Obstetrics and Gynaecology* 24, 2003, 31–38; Chan, R.W., Raboy, B., Patterson, C. «Psychosocial adjustment among children conceived via donor insemination by lesbian and heterosexual mothers». *Child Development* 69, 1998, 443–457.

the effects which are derived from the preeminence of the husband or of the male not united by a marriage bond. It configures a true “right to maternity” for women who are alone, eighteen years or older and of advanced age, homosexuals and *post mortem* fertilization. Thus, it has ceased to be a remedy for sterility to convert itself in the expression of the defense of the interests of women up to the point of setting up a new subjective right, in detriment of the protection of the child generated artificially: the right of a woman to reproduction.

The Law determines that the donation be anonymous and that it should guarantee the confidentiality of the identity data of the donors. Children born of donors only have the right of obtaining general information that does not include his identity. Only exceptionally, in extraordinary circumstances, that entail a certain danger for the life or the health of the child, could the identity be revealed and always with restricted character. Very different from the one that the Civil Code has in regards to the rights of adoptees to know their biological origins.

If the female is married she needs her husband’s consent –or of her stable couple- be the child theirs or not; its deals with the automatic filiation that determines as father who appears as husband in the Civil Register since a “presumption of paternity” exists.

Since women can legally be the user or the receptor of the techniques with independence of her civil state and sexual orientation, the possibility is opened of children without a father, be it they are children of a single mother or of two mothers. There is no legal father in these two cases where the possibility exists that the child can claim the paternity, since anonymity does not receive constitutional protection and, in contrast, the right to know one’s origins is, an integrated right in the free development of the personality of the child and in the protection of his dignity.

Homosexual couples have in the matter of assisted reproduction, the same requisites as heterosexuals. The child born resulting from heterologous fertilization would have the legal filiation of the female progenitor and of their spouse –a female that could legally only obtain maternity through adoption. If both females desired to share the maternity, by the ROPA technique (reception of the couple’s oocytes) and given that the recognition of the maternity is determined by the birth, it will be the uterine mother and not the biological that would have the legal acknowledgement.

8. Family relationships anchored in engendering

Family values –different from the values of other human relationships such as friendship, the sharing of the same nation, etc. - sink their roots in the biological level of the person.

The union of the personal bodies of a male and a female –the sole and specific union that permits *engendering*- implies the bodies and the loves, feelings, desires, donation..., etc. of both people. Such a union creates a human procreating space –not only physiological- in that the biological and personal level unites in such a way that when they engender the result is the person of their child: they configure the real and unchanged identity of the child. “Before and more profoundly than any other identity, we are children, siblings, fathers, or mothers, spouses---We are what we are, as relatives, we are it inside a relationship... Our family identities are relationships of unions¹⁰³.

The verb *engender* has a specific and rich content at both levels –the biological and of interpersonal relationships- of each human being. We cannot stop being the child of those that engendered us, nor sibling, or grandchild... With independence of being a good or a bad father, or a good child or a bad sibling, we are, and it is not permitted to us to stop being so even after death. Family relationships are intrinsic when *engendering*. It is intrinsic and essential because each human being is a familiar

¹⁰³ Viladrich, P.J. *El valor de los amores familia- res*. Ed RIALP, Madrid, 2005, 12 y ss.

being. Those relationships are not chosen, nor depend on nothing else. We are in them by our own right, naked of any other condition that is not being the link of that specific family chain of personal bodies that transmit the engendered life.

Although it would require explicitly and more profoundly than is possible in this context, it is true that the family ties, the texture of those intrinsic relationships of our own self, is “to give and to accept *“of ourselves”*... The most characteristic, inherent and exclusive of love and the communication in a family is what we give and what we accept *“our nature of body personal”*. Nothing more intimate for us than our own body. There is in this intimacy a love with a great and constant strength, a saber, the love for oneself... It is the love that each human person has, as an innate endowment, for his own self, for his own nature, for his own flesh and blood. That love for oneself to one’s own flesh and blood is the one that we share in family in two great and different lines. One is consanguinity: on grounds of begetting, they are of our *same* flesh and blood... Another is the conjugality: by free election...they have constituted themselves as if there were *the same flesh*¹⁰⁴.

The people, therefore, can foster in their family and adopt as children other people that are not of their carne and of their blood, and give them and share the affections of the family relationships. This, that has surely occurred since man has been man, does not detract from people; on the contrary they add a dose of humanity that diminishes the loneliness of those that are not surrounded by others of their carne and blood.

In assisted reproduction, “something” is lost forever. “Something” of different entity in the diverse forms of generating which we have dealt with in this article and that we perambulate now by way of conclusions.

1. A child generated from the gametes of a male and the woman infertile amongst themselves, living in a stable union, and committed in the upbringing and education is very similar to the child of one’s carne and blood. It is the same if the result of an insemination with the sperm obtained from a corporal union of the progenitors. What is lost? As the data shows, it is lost in the mother’s health and in the risks of life and the health of the children. It is not the same to heal infertility or an infertility that forces fertilization of some gametes that perhaps have anomalies and, thus, lack fertilizing power.

The procreating space that form the personal bodies of the parents and that determines the child’s identity, is at the same time the physiological space privileged by nature. It establishes a *natural filter* that selects between millions of sperm that, the best, capable of fertilizing the ovum well formed and matured in that feminine cycle. When they are artificially forced to mutually fertilize both gametes, it risks health. The ovary has to be stimulated in order to force fertilization. This has negative consequences for the mother’s health and for the life and health of the child. In the same manner that forcing fertilization requires handling the sperm, what has consequences on the child’s health, as is shown in the data that it is more effective the sperm insemination of a donor than with the husband’s semen that suffers some degree of infertility.

In turn, in the natural situation the engendered child goes through moments in which it is more vulnerable, the first stages of its life, in continuity physical in the privileged space of the mother that gestates it.

2. In the second place, the cascade triggers when the gametes are from donors, or the

¹⁰⁴ Viladrich, *op. cit.* 71, 35 -36.

generation of the gestation is separated, does not have limits. The pretension of the programs is of providing of the reinvented child the original project of paternity-maternity. The limits are set by biological level and only obviously in the negative sense. We have pointed out two shortcomings: the natural filter in the establishment of the biological relationships specifically between the gametes and the one of communication between the body of the mother and the body of the child at the start of its development.

The data contributed show that the model “invented” is biologically very inferior to the natural. The *in vitro* embryo, at most frozen, is in a very precarious vital situation and very exposed to an inhospitable environment. But by being placed off-site from the place that it corresponds to makes it more vulnerable, or makes it undergo a selection of tests, or that it can be in fact abandoned, does not mean that it is not a human being and therefore possesses the own personal character and specific of the individuals of the lineage of man. The manner that life is reached, nor the motives that have taken it to be generated, does not change its entity, nor detract humanity, is a human being.

All people are capable of perceiving the mystery of mankind: the disproportion between the fusion of the gametes of its progenitors and the result that is nothing less than a man endowed with intelligence, liberty, capacity to love, of personal relationships, of heroism and misery. Thus the results of this human experimentation, the failure of selecting the perfect baby, etc. could –should? – talk about the right of each human person to be engendered, without no one granting programming it from the outside. It should talk about the decision for a good therapy of sterility. To heal and prevent the factors- well known- bringing about an alarming decline in fertility.

3. The manner in the way that the ART have been implemented, ignoring the evident scientific objections, has created a public health problem that affects future generations. This is an intergenerational problem in the human double level. On the one hand, health problems of women to whom they have been that grant them reproductive rights without limits, health problems and fertility in the following generations. On the other hand, insoluble health problems of ruptures in vital family relationships for people and violated in test programs, experimenting against already solid evidence already of the damage that it entails.

An interesting book written by a French neonatal psychiatrist describes the questions that torment an imaginary only child that is born from a multiple transfer of embryos: Who me? Who has created my life? Why am I alive and my embryonic siblings are not? The feelings of powerful alternate with those of guilt for being the one that survived. Do I have siblings, cousins? What could I learn from them about myself?

All this should be thought once again and debated. Even hearing the opinion of those born in this way that go in entering in adult life and that they have much to say. It goes further on than what is understood by assistance to reproduction before infertility problems of a stable couple.