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AGE RELATED ETHICAL AND MEDICO-LEGAL ASPECTS OF *IN VITRO* FERTILIZATION (IVF)

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Abstract: Nowadays the average age of the first pregnancy in women has risen all over the world. With this increase come the decreased chances of obtaining a spontaneous pregnancy. The recent advances in artificial reproductive techniques have made it more possible for older couples to conceive. Age is considered the most important factor in determining the success rates in IVF (*in vitro* fertilization). In addition, availability of assisted reproduction techniques to older women and option of fertility preservation produced a growing demand for fertility services. The objective of this narrative review is to determine the age-related ethical and medical aspects regarding IVF. We performed a systematic review searching relevant information in PubMed using MeSH Terms such as: pregnancy, IVF, post-menopause women, advanced maternal age, fertility, pregnancy outcome. The results were then screened and included if they met the criteria to be written in English and containing information regarding ethical and medical aspects. The ethical landscape identifies a few distinguishable items like: "the unnatural" way of conception and relationship with the pre-embryo, the financial difficulties involved with these procedures, the relationship with malignancy and infectious diseases and patient's autonomy. Medical considerations discussed the use of younger donor oocytes to reduce the risks, as well as the higher risk for preeclampsia and gestational diabetes in women of advanced age, but with similar rates for miscarriage and multiple gestation. The results showed higher ethical and medical considerations in advanced maternal age, with possible involvement on the pregnancy and fetal outcome such as miscarriage, low birth weight or premature delivery. In conclusion, there is an overall positive attitude towards achieving pregnancy by IVF techniques in advanced maternal age with the possibility of donor oocytes. With respect to the medical complications that may arise, the consensus established that it involves higher risks for both mother and fetus, which can be mitigated by careful maternal screening and optimal maternal status.

Keywords: fertility, advanced maternal age, pregnancy, IVF (*in vitro* fertilization).

INTRODUCTION

Times have changed and nowadays the average age of first pregnancy in women has risen all over the world. There are various reasons for this late conception, among them being the entry of women in the work force, most of women being today carrier-oriented, the availability of effective, safe contraception and abortion services as well as the financial sustainability that comes with age. But, the first late conception is associated with decreased chances of obtaining a spontaneous pregnancy and the assisted reproductive technology (ART), including *in vitro* fertilization, has given hope to millions of couples suffering from infertility issues, creating at the same time ethical, medical and social controversies. That is how a new brand category of pregnant women appeared: the pregnancy at very advanced age.

Age is considered the most important factor in determining success rates after IVF, with the ideal IVF patient pool reported to be in the 26- to 30-year-old age range. Mid-life is defined by current literature between 40 and 65 years, but limits can be modified, taking into account the women's fertility, with lower limit starting at the age when there is a serious decline in fertility and upper age being defined by menopause. Natural fertility in female declines to <10 per cent after 40 years of age and spontaneous pregnancies are very rare after 45 years

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of age [1]. In addition to this fact, availability of assisted reproduction techniques (ARTs) to older women and option of fertility preservation have reinforced the idea of an infinite reproductive lifespan and produced a growing demand for fertility services. Not to forget that with increasing age, beside natural fecundity, the pregnancy rates after assisted reproduction decrease [2]; it is thought to be due to the ovarian aging, a decline in both quantity and quality of ovarian oocytes. It is generally known that the number of oocytes formed during fetal life decreases during women's reproductive period and as does the quality, explaining the fact that it is more difficult to obtain a pregnancy with autologous oocyte than with donor one at an advanced age. On the other side, use of young donor oocytes result in good pregnancy rates confirming the previous hypothesis [3-5].

Basal FSH level is another indicator for fertility referred as ovarian reserve [6]. While age is considered to have an independent effect on pregnancy after IVF and to be more related to the occurrence of an event, FSH level can be a better predictor of cycle cancellation and number of oocytes collected. Thus, patients with higher FSH levels are often advised to avoid IVF treatment, because the chance of success is thought to be low. A study conducted by van Kooij *et al.* in 2003 [4] showed that patients younger than 41 years of age with an elevated basal FSH level have a high probability of cycle cancellation owing to lack of ovarian response, but, if ovum pick-up and ET are possible, implantation and ongoing pregnancy are obtained. Regarding patients older than 40 years of age with FSH levels less than 15 IU/L, due to low quality of oocytes, their cancellation rate is higher because of no response. Furthermore, the implantation rate per embryo and the ongoing pregnancy rate are less than rates described before [7].

ETHICAL CONSIDERATIONS

The ethical landscape identifies a few distinguishable items such as "the unnatural" way of conception and relationship with the pre-embryo, the financial difficulties involved with this procedure, the relationship with malignancy and infectious diseases and patient's autonomy.

Issues regarding IVF

An ethically permissible behavior is based on the view that any decision is ethically permitted if it is voluntary taken and does not cause harm to others, as expressed by "Primum non nocere". IVF procedures are not without risks, most frequent under the form of multiple pregnancy, ovarian hyperstimulation syndrome, premature delivery and low birth weight, birth defects, ectopic pregnancy, miscarriage, and chromosomal abnormalities, increased with the maternal age. The number of pre-embryos that are transferred to the woman's uterus is determined by the chances of fertilization, and this varies with the woman's age. An adequate number of pre-embryos are needed to increase the likelihood of pregnancy. Nowadays, the tendency is to lower the number of transferred embryos to prevent multiple pregnancy which comes with its risks.

There is a discussion also regarding the augmentation of a natural process. In postmenstrual women Ekberg considers this procedure as "unnatural", disturbing the natural process of menopause [8-11]. De Wert is sharing the same opinion considering that IVF in postmenopausal women a reversal of the natural ageing process [9]. On the other side, there are critics, as Landau, that support the idea and see no ethical, medical or economical basis for denying the procedure to this category, unless it is restricted to women of all ages [11].

Financial difficulties

Given the fact that female age plays a crucial role in IVF outcomes, we aimed to highlight the economic implications of IVF outcomes. IVF in any population is considered both expensive and having a low success rate [12]. For older patients wishing to follow IVF treatment, counselling on success rates and financial costs is imperative, considering the even lower chances. Patients need to understand the financial consequences of incurred costs from cycle cancellations, higher drug dosages and the increased number of cycles required to achieve a live birth.

Age limiting

Establishing an upper limit for offering infertility services has its pros and cons. By setting an age limit we can manage the potential increased risk of maternal morbidity and mortality, risk of psychological and social burden on children and emotional barriers, hasty decisions or underestimated parenting needs. On the other side, an upper limit may narrow the fertile potential of a woman (to the average age of menopause e.g. India) and the reproductive autonomy, together with carrier concerns, but can increase the life expectancy in mothers giving birth at advanced age,

the family support and self-esteem, considering the fact that at younger ages is difficult to be self-financed [13]. Thus, women in their 20s and 30s should be counselled about the age-related risk of infertility when address for any reproductive health issues. Women > 35 years of age should be referred for infertility work-up after 6 months of trying to conceive. Ovarian reserve testing may be considered for women ≥ 35 years of age or for women < 35 years of age with risk factors for decreased ovarian reserve, such as a single ovary, previous ovarian surgery, poor response to follicle-stimulating hormone, previous exposure to chemotherapy or radiation, or unexplained infertility. Women > 40 years should consider IVF if they do not conceive within 1 to 2 cycles of controlled ovarian hyperstimulation, bearing in mind that the only effective treatment for ovarian aging is oocyte donation [14].

Cancer and other chronic diseases

Fertility preservation for individuals afflicted with cancer has important implications as often the chemotherapeutic agents used to treat cancer are toxic to the ovaries and result in diminished ovarian reserve and reduced fertility [15]. Beside all the technology developed, techniques for freezing oocytes and ovarian tissue are still considered experimental [16]. Regarding infectious diseases like hepatitis B, The Practice Committee of the American Society for Reproductive Medicine advises that sperm washing is not necessary to prevent sexual transmission risk as long as the female partner has been vaccinated. However, in ART, sperm washing is routinely used believing it could prevent introduction of the HBV into the oocyte [17]. Endometriosis is a common cause of infertility in women of all ages. Even in the presence of patent fallopian tubes, endometrial dysfunction and oocyte quality related to endometriosis-associated infertility, lead to an increased rate of IVF to achieve pregnancy [18].

The data in HIV patients performing IVF treatment is still conflicting, with not clear information if these patients display worsening outcomes per cycle comparing to the general population. Present literature does not present a difference in developing a pregnancy regarding woman's age. But, considering the higher rate of preterm birth and multiple gestations in IVF patients, elective single embryo transfer is better used [19].

Patient's autonomy

It is to mention the importance of autonomy in debates concerning health care ethics. Beside deciding over the beneficiaries and regulations of IVF procedure, we should take into account the emotional and psychological component of this procedure [20]. This results in weighing the autonomy of a post-menopause woman and the well-being of her future child. Obtaining a pregnancy at an advanced age comes with the risk of anxiety in the child over the impending loss of parents or becoming a caregiver for a parent at a young age, and even develop mental disorders associated to this fact, as mentioned in a Swedish study [21,22]. However, the positive aspect comes from parents being more committed to family life, wiser and more financially secured.

MEDICAL CONSIDERATIONS

Although artificial reproductive technology has helped millions of infertile couples, it comes also with risks and possible prejudice to the mother and future fetus. There is clear evidence of increased maternal morbidity and mortality, as well as variate risks regarding pregnancy evolution and fetal outcome related to maternal age.

When discussing about medical aspects involved in IVF treated patients of advanced age, it is important to mention a shared consensus about the uterine environment. Current literature indicates a context of receptivity and fertile environment of the uterus similar to a younger age even when ovaries become unable to provide gametes. A study performed by Sauer revealed that age- related decline in female fertility can be reversed by use of younger donor oocytes, with pregnancy rates similar to the young population [23]. Another study conducted by Paulson *et al.* on post-menopause women who used donor oocytes concluded that women over 50 years old were at risk for preeclampsia and gestational diabetes; the same group had a higher chance to deliver the children by C-section [12, 24].

As far as delaying childbearing period is becoming more common, it is recommended for this category of women to perform several analyses and investigations for a good pregnancy outcome. Prenatal screening, including genetic counselling, amniocentesis and frequent ultrasound examinations in order to assess early prenatal diagnosis should be part of a follow-up plan [25].

IVF involved the risk of multiple gestation if more than one embryo is transferred to the uterus being associated with the risk for low birth weight and premature delivery; for this reason, nowadays it is

preferred to use the single embryo transfer. Moreover, when both maternal and paternal ages are advanced, because of their ageing gametes, the conceived children are at higher risk for being low-birth weight [26]. Also, current studies showed that the rate of spontaneous abortion is similar in the group over 50 years-women with oocytes donor compared to the younger ones, at a rate of about 15% [8].

A comparison between women of advanced maternal age conceiving spontaneously (non-donor oocytes) and young women between 24 and 27 years old revealed greater risk of hypertension, gestational diabetes, chromosomal anomalies, and infants large for gestational age (LGA) which increases risks at delivery [27].

In conclusion, there is an overall positive attitude towards achieving pregnancy by IVF techniques in advanced maternal age with the possibility of oocytes donor. With respect to the medical complications that may arise in such pregnancies, the consensus revealed that it involves higher risks for both mother and fetus. Thus, this risk can be mitigated by careful maternal screening and optimal maternal status.

Although there are several ethical considerations regarding its use, ART, especially in perimenopausal women, it is a dynamic field of medicine that has managed to give hope and solutions to millions of infertile couples, with possibilities of continuous changes in the future.

Conflict of interest

The authors declare that they have no conflict of interest.

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