Med Law (2009) 28:565-575

Medicine and Law

Informed Consent

DONATION OF EGGS IN ASSISTED REPRODUCTION AND INFORMED CONSENT

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Abstract: In Spain, there exists an increasing amount of advertising for the donation of eggs for assisted reproduction. This study attempts to assess: (1) scientific evidence available about adverse effects of egg donation; (2) characteristics of the information given in the informed consent to donors; and (3) the legality of this advertising. The main results are: (1) Many severe problems are associated with induction of ovulation, as ovarian hyperstimulation (reported frequencies from 5.9 to 15%), thromboembolism, hepatic failure and increased risk of ovarian, breast, endometrial and colon cancer. (2) Informed consent for egg donors is very incomplete, according to the Spanish law 41/2002 on Patient's Information. (3) Current advertising to promote egg donation does not respect, among others, law 14/2006 about Assisted Human Reproduction, as it includes reference to economic compensation or benefits but no information about the risks. Deontological and judicial disciplinary procedures should be initiated to protect donors' rights.

Keywords: Egg Donation; Fertility Drugs; IVF; Ovulation Induction/ Adverse Effects; Ovarian Hyperstimulation Syndrome; Women's Health; Donor Payments; Quality Assurance; Spanish Law

INTRODUCTION

There exists an increasing amount of advertising for the donation of eggs by young women for reproductive purposes. This advertising is present in many types of posters which flood universities and youth centres. Advertisements are also published in newspapers and other mass media.

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In these posters and graphic media they call on the sense of "*generosity*" of these women, between 18 and 30, saying that couples will be able to have children if they donate their eggs. They also make reference to the fact that "*Your generosity will be rewarded*." We have confirmed both by consulting the centres themselves and by interviewing women who have donated their eggs, that they receive 600-1000 euros from the reproduction centres for undergoing the procedure of donating their eggs.

This phenomenon is well developed, shown by the fact that in vitro fertilization (IVF), using eggs donated by other women, has risen by 40% in Spain. The donation of eggs has doubled in only five years due to the delaying of maternity and the number of donors has multiplied by five in one year, according to the information collected by the assisted pregnancy company, Instituto Marquès de Barcelona. This same source asserts that women of 38-40 have usually used up their reserve of eggs contributing to a healthy child.

A donation of eggs implies pharmacological controlled ovarian stimulation, that is, an ovarian hyperstimulation that may develop into an ovarian hyperstimulation syndrome (OHSS)[1]. The OHSS is a potentially life-threatening complication of ovulation treatment and is considered responsible for the majority of IVF cycle-related complications[2]. Severe forms are characterized by a massive ovarian enlargement with the formation of multiple ovarian cysts associated with extravascular fluid shifts resulting in the development of ascites, pleural and/or pericardial effusion. The clinical course of OHSS may involve, according to its severity and the occurrence of pregnancy, electrolytic imbalance, neurohormonal and haemodynamic changes, pulmonary manifestations, liver dysfunction, hypoglobulinaemia, febrile morbidity, thromboembolic phenomena, neurological manifestations and adnexal torsion[3]. In its severe form, the patient needs to be admitted to hospital, strictly monitored and given supportive treatment until the

1. Delbaere, A., *et al.*, Understanding ovarian hyperstimulation syndrome. *Endocrine*, 2005. 26(3): p. 285-90.

2. De Sutter, P., J. Gerris, and M. Dhont, Assisted reproductive technologies: how to minimize the risks and complications in developing countries? *Hum Reprod*, 2008.

3. Delvigne, A. and S. Rozenberg, Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). *Hum Reprod Update*, 2003. 9(1): p. 77-96.

problem resolves itself or the woman dies[4, 5]. The pathophysiology of the syndrome has not yet been completely elucidated.

The pharmacological agents that are used in the stimulation of the ovaries include clomiphene, bromocriptine, gonadotrophin preparations and gonadotrophin-releasing hormone (GnRH) and its analogues[6]. Each agent is associated with its own specific adverse effects, and all of them may cause OHSS when used in the induction of ovulation[3]. According to the literature, the most common form of OHSS occurs a few days after follicular rupture or puncture, when follicular growth has been medically induced by using either clomiphene citrate (CC) or gonadotrophins, sometimes in conjunction with GnRH agonists or antagonists, and following final follicular maturation and luteinization achieved by administration of hCG[3].

Gonadotrophin therapy is supposed to lead more frequently to OHSS. However, it has been published that the protocols in the repeated use of gonadotropins in small doses produces a lower frequency in cases of OHSS[7]. Another agent, CC, is a selective estrogen receptor modulator drug that is used for induction of ovulation in women, specially if they suffer any kind of infertility such as polycystic ovarian syndrome. CC caused OHSS less frequently than ovulation induced by gonadotropins[7]. CC has been associated with hot flushes, visual disturbances, cervical mucus abnormalities and luteal phase deficiency. Similarly, most of the adverse symptoms associated with bromocriptine are short-lived, such as nausea and postural hypotension.

Lastly, modern and more reliable GnRH antagonists such as cetrorelix and ganirelix are now used in controlled ovarian hyperstimulation because their incidence of OHSS is less than with gonadotropins analogues[8]. It is also used

4. Schenker, J.G. and Y. Ezra, Complications of assisted reproductive techniques. *Fertil Steril,* 1994. 61(3): p. 411-22.

5. Delvigne, A. and S. Rozenberg, Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Hum Reprod Update,* 2002. 8(6): p. 559-77.

6. Derman, S.G. and E.Y. Adashi, Adverse effects of fertility drugs. *Drug Saf,* 1994. 11(6): p. 408-21.

7. Hamilton-Fairley, D., *et al.*, Low-dose gonadotrophin therapy for induction of ovulation in 100 women with polycystic ovary syndrome. *Hum Reprod,* 1991. 6(8): p. 1095-9.

8. Al-Inany, H.G., A.M. Abou-Setta, and M. Aboulghar, Gonadotrophin-releasing hormone antagonists for assisted conception: a Cochrane review. *Reprod Biomed* Online, 2007. 14(5): p. 640-9.

for the prevention of severe OHSS in the procedure of "coasting", by withdrawing both gonadotropins and GnRH agonists[9].

OBJECTIVES

Due to the possible harm to the rights and health of young people submitted to these techniques without the proper information, this study attempts to review the scientific literature for the following:

1) The scientific evidence available about the possible adverse effects of egg donation for assisted reproduction.

2) The characteristics of the informed consent offered to the donors by the centres which undertake such procedures.

3) The possible limits to the legality of advertising about egg donation.

RESULTS

1) Review of the possible adverse effects of egg donations for assisted reproduction.

The first risk that must be pointed out is that egg donors have the possible risk of an ovarian reserve decrease in the future, although this has not been definitely proved[10].

Recent studies stated that in the absence of sufficiently large numbers of egg donors to assess the risk of OHSS, comparative data should be obtained from women undergoing similar superovulation protocol for IVF when available[11].

Studying high quality scientific journals of the last few years, we find that the ovarian hyperstimulation which these young women undergo poses a potential risk which is yet to be defined. In 1998, Serour and collaborators summarised the medical complications of assisted pregnancy in 3500 cycles (2942 patients)

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9. Moon, H.S., *et al.*, Short coasting of 1 or 2 days by withholding both gonadotropins and gonadotropin-releasing hormone agonist prevents ovarian hyperstimulation syndrome without compromising the outcome. *Fertil Steril*, 2008.

10. Serna, J. and J.A. Garcia-Velasco, Effect of repeated assisted reproduction techniques on the ovarian response. *Curr Opin Obstet Gynecol*, 2005. 17(3): p. 233-6.

11. Jayaprakasan, K., *et al.*, Estimating the risks of ovarian hyperstimulation syndrome (OHSS): implications for egg donation for research. *Hum Fertil* (Camb), 2007. 10(3): p. 183-7.

in the Egyptian centre Centre-Cairo[12]. The complications of the procedure that they published were: moderated OHSS in 5.9%, severe OHSS in 1.7%, vaginal bleeding in 0.9%, pelvic infection in 0.3%, deep vein thrombosis in 0.11%, hemiparesis in 0.06%, acute abdomen in 0.9%, anaesthetic complications in 0.06%, and the death of one patient (0.03%). Other complications described in this Egyptian centre were ovarian cancer in 0.06%, carcinoma of the breast in 0.03%, thyroid adenoma in 0.03% and breast adenoma in 0.03%.

The prestigious Cleveland Clinic Foundation and a Belgian team have recently advised the scientific world of the danger of these techniques for eggs donors, suggesting that OHSS may be serious and even fatal[1, 13]. The scientific community is as yet unsure of the ultimate cause of OHSS and disagree over the frequency with which women can suffer from these problems: centres which use these techniques suggest about 5%, but the number of affected could be more than 10%[4, 5]. In a prospective study developed by Newcastle Fertility Centre at Life, and published in 2007, they concluded that if an egg donor develops 20 follicles or more, her risk of hospital admission due to OHSS is high, but less than 15%[11]. They pointed out that the absence of pregnancy in egg donors did not eliminate the risk of OHSS. They recommended that egg donors who develop 20 follicles or more should be actively monitored for the first week after egg collection.

Apart from the OHSS, the Polish gynaecologist Obrzut and collaborators reported in 2005 the existence of a serious hepatic dysfunction associated with the induction of ovulation[14]. An IVF centre and the Free University of Brussels in 2003 warned that the stimulation to produce eggs could cause serious pulmonary, neurological and haematological complications, amongst others[3].

12. Serour, G.I., *et al.*, Complications of medically assisted conception in 3500 cycles. *Human Reprod.* , 1998. 13(Abst. book I. Abst. No. 156.).

13. Budev, M.M., A.C. Arroliga, and T. Falcone, Ovarian hyperstimulation syndrome. *Crit Care Med*, 2005. 33(10 Suppl): p. S301-6.

14. Obrzut, B., *et al.*, Liver dysfunction in severe ovarian hyperstimulation syndrome. *Gynecol Endocrinol*, 2005. 21(1): p. 45-9.

A pioneer Taiwanese group has described cases of serious thromboembolism and from London there have been described cases of deafness[15, 16].

Looking now at the most serious effects such as cancer, there are many studies that may result from the epidemiological link. Researchers from the University of New York have indicated that ovarian hyperstimulation seems to be related to ovarian cancer and a Serbian group has published cases in which patients have suffered fatal cancer following the induction of ovulation and in vitro fertilisation[17, 18]. Furthermore, an extensive study which considered 3837 women treated for infertility between 1974 and 1985, emphasized that the use of the CC for a prolonged time could increase the risk of ovarian cancer[19]. Moreover, the National Institute of Health developed an study in 2003 which showed that the risk of breast cancer amongst women who take medication containing gonadotropins is two or three times greater than that of women who have never taken medication for fertility treatment, and other studies also confirm this association[20, 21]. Nevertheless, there are other studies that do not find a breast cancer association with IVF techniques[22, 23]. The link between CC and

15. Onalan, G., *et al.*, Empty follicle syndrome in two sisters with three cycles: case report. *Hum Reprod*, 2003. 18(9): p. 1864-7.

16. Ou, Y.C., *et al.*, Thromboembolism after ovarian stimulation: successful management of a woman with superior sagittal sinus thrombosis after IVF and embryo transfer: case report. *Hum Reprod*, 2003. 18(11): p. 2375-81.

17. Lukanova, A. and R. Kaaks, Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. *Cancer Epidemiol Biomarkers Prev*, 2005. 14(1): p. 98-107.

18. Milenkovic, V., *et al.*, [Ovarian cancer after in vitro fertilization]. *Srp Arh Celok Lek*, 2004. 132(9-10): p. 331-3.

19. Rossing, M.A., *et al.*, Ovarian tumors in a cohort of infertile women. *N Engl J Med*, 1994. 331(12): p. 771-6.

20. Burkman, R.T., *et al.*, Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. *Fertil Steril*, 2003. 79(4): p. 844-51.

21. Pappo, I., *et al.*, The possible association between IVF and breast cancer incidence. *Ann Surg Oncol*, 2008. 15(4): p. 1048-55.

22. Casper, R.F., Aromatase inhibitors in ovarian stimulation. *J Steroid Biochem Mol Biol*, 2007. 106(1-5): p. 71-5.

23. Salhab, M., W. Al Sarakbi, and K. Mokbel, In vitro fertilization and breast cancer risk: a review. *Int J Fertil Womens Med*, 2005. 50(6): p. 259-66.

endometrial cancer result is more consistent, and recent studies showed increased risks[24-26]. Recently, there was published a case report of fatal colon cancer in a young, previously healthy woman 4 years after repeated ovarian stimulation for egg donation[27].

2) The characteristics of informed consent offered to egg donors in the centres which carry out this technique:

Those egg donors who elect to take risks for others require meaningful assurance that unpleasant outcomes amongst donors have not gone unreported or been under-reported because the majority of studies center on the effects of the women who undergo a IVF treatment[28].

As we will explain, informed consent in IVF centres is incomplete as far as the information which, by law, must be provided for women according to the law 41/2002 on Patient's Information in Spain. The act of 41/2002 completed what was related to the information to patients in the act 14/1986, which is the Health General Act of Spain. The correct consent is defined in the act 41/ 2002, article 3, by "*the free and conscious conformity of a patient that is expressed in his correct faculties, after having received the appropriate information, so that there could be an incident that affect his health*". In article 10 of the act 41/2002 it is stated that the patient has the right of knowing "*(1) the main consequences that will surely originate the intervention; (2) the risks that he suffers and that are related with the personal and professional circumstances of the patient; (3) the probable risks in normal conditions, according with the experience and scientific status, that are directly related with this type of intervention; (4) the contraindications*."

24. Brinton, L., Long-term effects of ovulation-stimulating drugs on cancer risk. *Reprod Biomed Online*, 2007. 15(1): p. 38-44.

25. Rimon, E., *et al*., Gonadotropin-induced gene regulation in human granulosa cells obtained from IVF patients: modulation of genes coding for growth factors and their receptors and genes involved in cancer and other diseases. *Int J Oncol*, 2004. 24(5): p. 1325-38.

26. Venn, A., *et al*., Characteristics of ovarian and uterine cancers in a cohort of in vitro fertilization patients. *Gynecol Oncol*, 2001. 82(1): p. 64-8.

27. Schneider, J., Fatal colon cancer in a young egg donor: A physician mother's call for follow-up and research on the long-term risks of ovarian stimulation. *Fertil Steril*, 2008.

28. Ahuja, K.K. and E.G. Simons, Cancer of the colon in an egg donor: policy repercussions for donor recruitment. *Hum Reprod*, 1998. 13(1): p. 227-31.

The doctor has to explain personally all the information to the patient and informed consent must be also written for the following interventions: surgical interventions, invasive diagnostic and therapeutic procedures, and, in general, the procedures that implies risks or inconvenience that could have a probable negative effect on the patient´s health. So, according with the current legislation in Spain, the informed consent is a legal document that gives enough information in order that a patient knows the alternatives, consequences of the intervention, percentage of side effects and major and minor contraindications. In fact, the informed consents for surgical interventions are usually extensive and include, in percentages, every side effect that may occur after that procedure.

To understand the characteristics of informed consent offered to egg donors in Spain, a study has been made of informed consent according to the Spanish Fertility Society or certain private centres such as "FIV Madrid". In both cases examined they are not exhaustive in laying down all the serious side effects than can occur due to ovarian stimulation, saying that OHSS appears in "*less than 1% of cases*", a scientific fact which we have shown is not exact. Furthermore, in these informed consents they flatly deny the most probable relation between ovarian stimulation and ovarian tumors.

A study published by the British Cromwell Hospital states that doctors should inform IVF patients or egg donors - prior to obtaining their consent for IVF treatment - of the possible risks they may suffer and specially, egg donors should be informed about the link of this procedure with cancer[28].

In some countries, as in the United Kingdom, the national regulatory body, called Human Fertilisation and Embryology Authority have compared egg donation to blood donation or even sperm donation[28]. It should be pointed out that, being both the donation of gametes, egg donors are not equally exposed to the same risks as sperm donors. The informed consent in sperm donation or blood donation do not have to include any reference to severe affection of the health, death or cancer.

3) The study of the possible limits to the legality of advertising about egg donation.

Unlike, India, the USA, and Canada, gamete donors cannot be paid in Spain and other countries such as Israel, Australia, Denmark, France, the UK, and Denmark. The only way to promote the IVF treatments in Spain is that private medical centers advertise the possibility of egg donation.

To our knowledge, the advertising which is being used to promote egg donation does not respect medical deontology. The Code of Ethics and Medical Deontology of Spain, whose last edition was in 1999, indicates in article 38.1 that "*advertising must be objective, prudent and truthful, in that it does not raise false hopes or promote unfounded concepts*." To be objective means to be simply explanatory of the product, medical speciality and method of contact. Objective, in this sense, also means the absence of any misleading information directed towards young potential egg donors.

When referring to advertising, the Spanish Code of Ethics and medical deontology doctrine includes advertising of clinics, therapeutics, medical services and also donation of blood or other tissues. In the case of giving blood by healthy people, the advertising aimed at stimulating an altruistic donation is justified. There is no serious health risk in the act of giving blood, as long as the donor has been examined to check his general health and is found to be within adequate weight and age ranges.

The Spanish College of Doctors (Organización Médica Colegial) has the duty to ensure that the 'medical quality' standards of advertising are much higher than those established by civil laws, as medicine has nothing to do with commercial activities. That is why in 1996 the Spanish College of Doctors published an official document called *"Deontological rules on medical advertising*". Every advertisement that is authorized by the Deontology Commission of the College must show an indication of its approval.

Regarding Spanish civil law, in article 4 and 5 of the General Law of Advertising of Spain - 34/1988 law - it is indicated that all deceptive or prescribed advertising is "*illegal*", meaning that which does not offer all the information about the harmfulness or dangerous effects of the object being advertised.

Illegal is, in our opinion, the legal status of this advertising that promotes egg donation in Spain. In our specific case, young women are not merely informed, but they are attracted by these advertisements of IVF centers. These ads usually show young women or parts of a female body and mention "*generosity*" and economic *"reward"*, which are positive items, but do not really explain what may imply the act of egg donation. At no time in the posters and media advertisements do those responsible for these private IVF centers state the possible fatal effects of the procedure, both in the short and long terms.

Lastly, we have confirmed, both by consulting the centres themselves and by interviewing women who have donated their eggs, that the IVF centers offer

600-1000 euros for undergoing the intervention and procedure of donating their eggs. This donation of an economic reward by IVF centers is contemplated in law 14/2006 about Assisted Human Reproduction, which substituted the former law in this area, that is law 35/1988. Article 5.3 of law 14/2006 states that "*the donation (of gametes) will never have a lucrative or commercial characteristic. The economic compensation that could be stipulated only may compensate the physical troubles and the travel costs and labour costs that may be derive from this donation and never should be an incentive for this. Any advertisement or promotion of donation of gametes from authorized centers should respect the non-profit character of the donation, being forbidden to promote the donation by means of economic compensations or benefits*".

According to the Spanish Assisted Human Reproduction Law, the advertisements that IVF centers are developing do not follow theses statements, as they clearly include the existence of an economic reward or compensation hidden in the appeal for donation of eggs by young women.

CONCLUSIONS

To our knowledge, there has been no systematic study of the long-term risk of cancer or other adverse outcomes in healthy egg donors, but the risks are normally extrapolated form those of women who undergo IVF treatment in order to get pregnant.

As it is practically essential to use egg donation to achieve a pregnancy through assisted pregnancy using IVF treatment, it will be necessary to make this procedure suitable and in accordance with the current law on informed consent and the advertising of medical procedures. At present, we consider that potential egg donors cannot give truly informed consent because insufficient information exists about their possible long-term risks.

We conclude, therefore, that it is unacceptable, from the point of view of medical deontology, that the IVF centres be undertaking these advertising campaigns by the means of posters, newspapers and other means of communication. The mechanism of ovarian stimulation and the possible occurrence of OHSS imply that the process can be potentially very harmful to young women. We have tried to show in this article that the type of advertisement that promotes the donation of eggs does not follow the relevant provisions of current civil law.

We hope that deontological and judicial disciplinary procedures are initiated,

with the aim of improving the rights to information and health of women who donate their eggs.