THE EVOLUTION OF PREGNANCIES FOR THE PATIENTS WITH POLYCYSTIC OVARY SYNDROME AND OVARIAN HYPER STIMULATION SYNDROME

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Abstract. The ovarian hyper stimulation syndrome (OHSS) is a feared complication during the controlled ovarian simulation process. In this study we followed the evolution of pregnancies for the patients diagnosed with polycystic ovary syndrome (PCOS) after they had previously undergone a controlled ovarian stimulation, using different protocols, therapy that was complicated by the syndrome of hyper stimulation. The group of participants in the study included 46 patients that were diagnosed with OHSS, aged between 25 and 39, over a period of 4 years (2011-2014). If the risk of OHSS is high, we will not use human chorionic gonadotropin (HCG) to trigger ovulation. The protocols must be carefully individualized and the stimulation cycles need to be correctly monitored. The evolution of the pregnancies with OHSS can be to term, giving birth to living eutrophic foetuses (30 patients), or there can be premature labour, before the term (8 patients – 21.1%).

INTRODUCTION

The incidence of OHSS for the women treated with Clomiphene citrate (CC) is hard to find out, because the definitions given to the syndrome are very different from one study to another. While mild OHSS (moderate increase of the ovaries) is relatively common, severe OHSS (a massive increase of the ovaries, progressive weight gain, severe abdominal pains, nausea and vomiting, hypovolemia, ascites and oliguria) is only rarely observed.

The necessity of ovary stimulation appears when there is a diagnostic of ovulatory dysfunction, which can be established by menstrual history, a regular determination of serum progesterone (during the presumptive luteal phase), monitoring the urinary excretion of pregnanediol or through periodical transvaginal ultrasound scanning. The specific ovulation tests are useless when the menstrual history can establish the diagnostic (amenorrhea, oligomenorrhea). Once identified, infertile women, with no ovulation, deserve further evaluation before the treatment, in order to identify any other systemic diseases that would require further investigation, counselling or specific treatment. Establishing a detailed medical history and physical examination can also show other endocrine or metabolic diseases. It is justified to perform a screening for hypothiroidism, serum level for thyroid-stimulating hormone (TSH) and for hyperprolactinemia because both diseases are treated better with other medication than CC. Ovarian failure assessment is recommended for all amenorrhoeic women, regardless of age. Screening for impaired glucose tolerance or diabetes is recommended for obese women (body mass index BMI >30 kg/m2) with PCOS (Cuellar F.G, 1980; Lincoln S.R., 1999; Practice Committee of the American Society for Reproductive, 2004).

Another cause is PCOS (polycystic ovary syndrome). Pre-conception counselling for the women with PCOS should identify the risk factors for reproductive failure and should correct them before starting a treatment. It is essential to admit the presence of obesity and its centripetal distribution that can vary depending on ethnicity and geographical area and to recommend a supplement of folic acid for all the women, and also to recommend them to quit smoking. It is a well-known fact that obesity is associated with anovulation (Pasquali R., 2006), miscarriage (Heijnen E.M., et al, 2006) and the complications appeared in the last trimester of pregnancy (preeclampsia, gestational diabetes) (Boomsma C.M., et al, 2006). Pasquali states that the role of losing weight in managing PCOS should be encouraged before any pharmacological treatment (Pasquali R., 2006).

The logical treatment of the women with PCOS is to induce ovulation, in particular by administration of CC, and in case it does not work, by treatment with exogenous gonadotropins. The main complication of inducing ovulation is the rate of 10% of multiple pregnancies, especially following the treatment with gonadotropins. For this reason, the use of gonadotropins can be questioned (van Santbrink E.J., 2003). If there is no body weight loss and the treatment with anti-oestrogens or ovarian drilling does not work, we can argue that inducing ovulation with the help of the treatment with exogenous gonadotropins must be replaced by ovarian stimulation and IVF (*in vitro* fertilization) hence the risk of OHSS.

PURPOSE AND OBJECTIVES

The purpose of inducing ovulation to the women with anovulation caused by PCOS is to re-establish fertility and to result in a living new-born. The method of inducing ovulation through therapy with gonadotropins is based on the physiological concept according to which initiating and maintaining follicular growth can be obtained with a transitory increase of FSH (follicle stimulating hormone) over a threshold-dose, for a period of time long enough to generate a limited number of developing follicles. It is essential to apply this concept ovulation is induced to women with PCOS, because they are specifically predisposed to an excessive development of multiple follicles.

MATERIAL AND METHODS

The study group included 46 patients diagnosed with PCOS, aged between 25 and 39, over a period of time of 4 years (2011-2014).

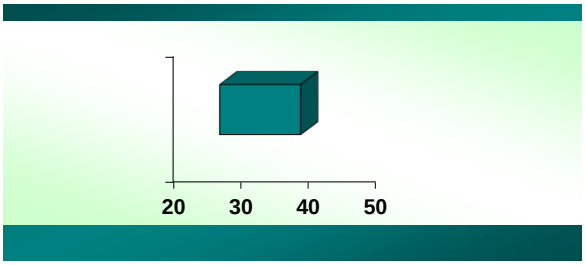

Fig. 1. *The mean age of the patients included in the study*

The observation sheets of the hospitalized patients were monitored and the data supplied by them was processed. Thus it was possible to interpret the: age of the patients, social background, diagnostic when admitted, reasons for hospitalizing them, the way in which the illness started, personal physiological priors (history), personal pathological history, clinical examination, ultrasound, blood analysis, surgical intervention, pathology data, evolution and complications.
After establishing the diagnostic of **infertility and PCOS**, the doctors discussed the options and methods of treatment with every couple. At this moment there is a wide range of such options. You can choose a passive attitude, of waiting or you can choose one of the following once ovulation is induced: controlled ovarian hyper stimulation, intrauterine insemination, vitro fertilization, intracytoplasmic injection of sperm, using gametes or embryos, or surrogate mothers. Ovarian stimulation has an important role in the treatment of assisted human reproduction.
The criteria for accepting somebody in the study group were given by the appearance of the hyper-stimulation syndrome, in different degrees, for the patients with a positive pregnancy test. So, of the initial 46 patients that were initially included in the group, 38 had pregnancies following controlled ovarian stimulation, the rest of 8 did not get pregnant, but only developed a mild or moderate form of OHSS.
Clomiphene citrate was administered orally, for 5 days, starting with the second to the fifth day after the beginning of their menstrual cycle that appeared spontaneously or induced by progestogenes. The ovulation rates, the conception rates and the results regarding the pregnancy are similar, no matter if the treatment begins in the second, third or fourth day of the cycle (Practice Committee of the American Society for Reproductive, 2004). Although the dose that is necessary to obtain ovulation is correlation with body weight, there is no certain way of predicting accurately the dosage that is necessary for each woman. These medicines can be used only if the hypothalamic-pituitary axis works. The main factors that predict the negative result of the treatment are: obesity, hiperandrogenemia and age (Imani B., et al, 2002). The ovarian volume and the menstrual state are supplementary factors that help to predict the reaction to CC (Eijkemans M.J., et al, 2003).

RESULTS AND DISCUSSION

Of the 38 patients with PCOS who got pregnant, 29 patients had a mild form of OHSS, and 9 patients had a moderate form.

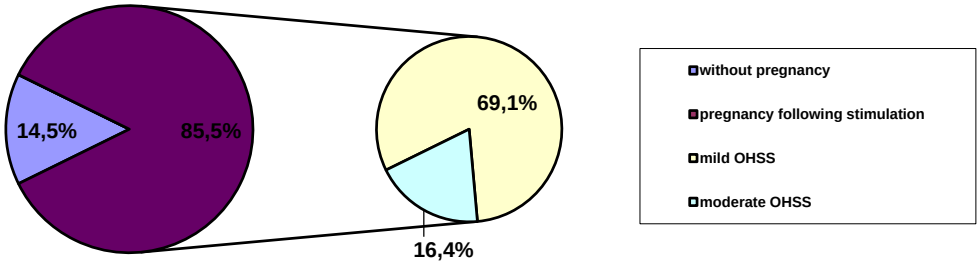

Fig. 2. *The structure of the group based on the presence of pregnancy following stimulation*

Of the 8 patients with PCOS who did not result in a pregnancy, 6 had a mild form of OHSS, and two patients had a moderate form.

As clinical symptoms, the pregnant women with mild forms of OHSS showed abdominal discomfort and distension, an increase in the size of the ovaries that was shown by ultrasound, with multiple follicles, estradiol dosed to values over 3000pg/ml, progesterone over 30pg/ml.

The first line therapeutic conduct was one of waiting, the patients with mild forms being monitored over a period of time of about 10 days for blood pressure, pulse, weight, and diuresis. In these cases, the clinical picture was delivered in 5-7 days.

The 9 pregnant patients with a moderate form of OHSS showed the following symptoms: ascites, urine retention, and dyspnoea, a significant increase in body weight and changes in the biochemical samples. They required close monitoring of blood pressure, diuresis, pulse, body weight and biochemical values, plus the degree of ascites. The patients were recommended bed rest and oral hydration.

None of the cases required a transvaginal puncture of Douglas pouch. Urine retention was signalled for 2 patients, with a diuresis of 100-200ml/day, considering a parenteral hydration of 2000-2500ml/day; in these cases we used furosemide for treatment.

All the cases of OHSS - moderate form – were treated with albumin for obtaining a hydro electrolytic balance.

The clinical picture was made after 14-21 days.

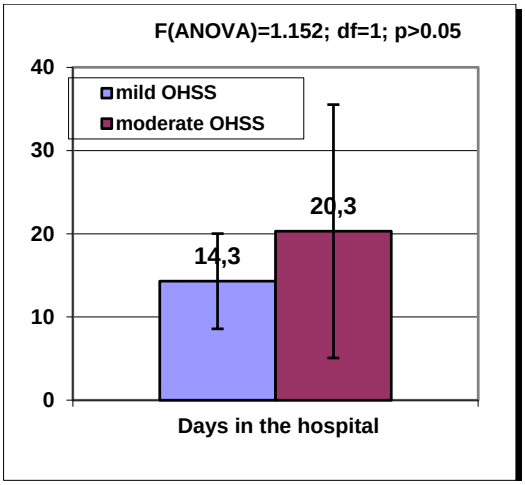

Fig. 3. *The mean number of days spent in the hospital depending on the clinical form of OHSS*

The evolution of the cases was favourable, as no patient required her pregnancy to be terminated. Of the total number of pregnancies studied, 8 delivered the baby before 36 weeks.

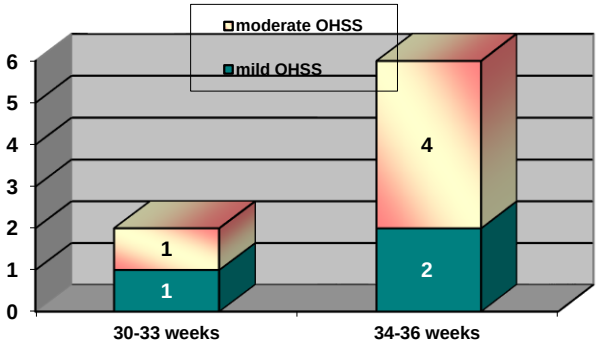

Fig. 4. *Gestational age based on the clinical form of OHSS*

According to a cohort study, *The Australian Longitudinal Study on Women's Health* (ALSWH): the prevalence of PCOS was of 5,8% (95% confidence interval CI: 5,3%-6,4%); infertility was claimed for 72% of the patients with PCOS in comparison with 16% for the general population (p‹ 0,001); hormone treatments were necessary in 62%, n=116 in comparison with the general population - 33%, n=162, (p‹0,001) – the rate of IVF (in vitro fertilization) was similar (Bates G.W.& Legro R.S., 2013).

In a random study, the rates of births were not different for the women treated only with CC, in comparison with the ones treated with CC and metformin (Nestler J.E., et al, 1998). In the case of the patients who do not succeed to ovulate with CC, metformin was shown to improve the ovulation and pregnancy rates in comparison with the response to CC. Many controlled random studies

showed that pre-treatment with metformin in doses of 1500 to 1700 mg per day significantly improved the ovulation and pregnancy rates in response to the administration of CC to the women who did not succeed to ovulate only with CC (Fernandez H., 2011; Zreik T.G., et al, 1999). For the obese women who did not respond to therapy with CC or for the couples who did not consider pregnancy an immediate purpose, metformin combined with diet and physical exercise for losing weight might be considered (Imani B., 2002).

HMG-human menopausal gonadotropin and pure filitropin (FSH) are the gonadotropins that are approved in treating PCOS. HMG contains 75UI FSH and 75UI LH and it is obtained from the urine of the women at menopause. FSH is obtained either from urine (uFSH), or through genetic engineering (rFSH), with no LH activity (Amin M., 2003, Krysiak R., 2006, Pritts E.A., 2002). The disadvantages of using gonadotropins for the patients with resistance to citrate of clomiphene are represented by the high costs and the risk of developing the syndrome of ovarian hyper stimulation and multiple pregnancies (Hoyt K.L., 2004). There is no data to compare directly the rates of ovulation and pregnancy with the ones obtained only with gonadotropins. The advantages of a combined therapy with CC and gonadotropins include a reduced dose of gonadotropins and a potentially decrease in the monitoring costs. The women with anovulation that are resistant to clomiphene citrate are often very sensitive to small doses of gonadotropins, and the treatment should have as main purpose the obtaining of one mature follicle every time this is possible, because, leaving IVF aside, there is no sign of deliberate supra-ovulation for the infertile women with anovulation. The alternatives to CC therapy for women who are resistant to CC include aromatase inhibitors, tamoxifen, insulin-sensitizing agents, laparoscopic ovarian drilling, the use of gonadotropins and IVF.

The most frequent complications of gonadotropin therapy are due to multiple ovule maturation, ovarian hyper-stimulation and multiple pregnancies. Women with polycystic ovary syndrome and anovulation are like to grow more follicles when they are given gonadotropins.

Heijnen et al. (2006), showed that the rate of menstrual cycle stopping is significantly higher for the patients with PCOS (12.8% versus 4.1%; RR 0.5; CI of 95%, 0.2-1.0). The stimulation lasts significantly longer for the patients with PCOS (1.2 days; CI of 95%, 0.9-1.5), even when the daily dosage of FSH is similar with that for the patients without PCOS. There were significantly more complex cumulus oocytes obtained (2.9; CI de 95%, 2.2-3.6) from the women with PCOS, but the fertilization rates were similar with those of women without PCOS. When referring to the probability of a pregnancy, the rate of clinical pregnancies for every cycle was similar (≈ 35%) for the patients with PCOS and those who do not have PCOS. The same thing applies for the pregnancy rate when harvesting oocytes and the embryo transfer. For the moment we lack the specific data regarding the rate of success of the transfer of one embryo to the women with PCOS. There are some proofs that show that supplementary use of metformin can improve the chances for an ongoing pregnancy and can reduce the incidence of PCOS. The most important complication of ovarian stimulation is OHSS. Still, there is no solid data regarding the incidence of OHSS in women with PCOS that undergo ovarian stimulation with the purpose of getting IVF.

CONCLUSIONS

OHSS (ovarian hyper stimulation syndrome) appeared in the case of the patients diagnosed with PCOS (polycystic ovary syndrome) who underwent a controlled ovarian stimulation.

Dopamine agonists will be used on the patients with a risk of OHSS.

Ovulation is triggered only after the level of estradiol is known.

Oocytes cryopreservation is the only method of preventing late OHSS and will be used if the number of oocytes is over the accepted threshold.
It is important to rigorously monitor the patients with an excessive ovarian response.
OHSS (ovarian hyper stimulation syndrome) is more intense for the patients with an associated ongoing pregnancy.
When analyzing OHSS (ovarian hyper stimulation syndrome) that is associated with pregnancy it is important to follow the parameters with the purpose of obtaining a physiological plasma volume and to correct electrolyte imbalances.
The intention is to use a treatment protocol for the patients who had IVF that will impose a conduct to follow in order to get and maintain a viable pregnancy when there is OHSS present. All IVF clinics must have protocols for identifying the patients with OHSS risk and to have limits for the values of estradiol and oocytes harvested in order to prevent OHSS.
Regardless of the clinical form of the syndrome, pregnant women will be hospitalized and treated like pregnant women with an increased obstetrical risk.
The evolution of pregnancies that associate OHSS can be to term, giving birth to living eutrophic foetuses, (30 patients) or can result in premature labour, before term (8 patients).
Thus, in our group, the incidence of premature pregnancies was 21.05%.

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