CONTROLLED OVARIAN HYPERSTIMULATION AND IVF PREGNANCY PROGNOSIS

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CONTROLLED OVARIAN HYPERSTIMULATION AND IVF PREGNANCY PROGNOSIS (Abstract): IVF (in vitro fertilization) often represents the ultimate step in our attempt to treat infertility. Nowadays this method is more and more used; couple’s expectations are higher and higher, so that optimizing the chance that one IVF pregnancy became a healthy newborn child is becoming an important issue. In this study we analyzed the controlled ovarian hyperstimulation impact on IVF pregnancy prognosis. We studied 307 patients who had IVF fresh procedures in “Panait Sirbu” Clinical Hospital of Obstetrics and Gynecology - Department of Assisted Human Reproduction between 01.01.2008 – 31.12.2010 and obtained pregnancy; pregnancy rate according to our statistics is 34%. For statistic analysis we used the odd Student test. Our data proved better results (defined as a better birth/abortion ratio) for the patients where recombinant FSH was used towards patients where highly purified urinary gonadotropin or the combination of the two drugs was used. Our statistical data also proved that none of the variables: age, BMI (body mass index), endometrium thickness, number of oocytes, number of embryos or number of days of stimulation is a favorable variable for this better result, but the number of units of gonadotropin is a favorable variable for a better birth/abortion ratio. We consider that our data gives an interesting perspective upon the connection between controlled ovarian hyperstimulation and pregnancy outcome, especially these days when tendencies are to obtain as many oocytes in one procedure as we can, which often means to use high doses of gonadotropin. Keywords: IN VITRO FERTILIZATION, CONTROLLED OVARIAN HYPERSTIMULATION, PREGNANCY, PROGNOSIS.

Nearly 13-15% of reproductive aged couples are infertile (1). Infertility is a real health problem; it is always associated with emotional stress and affects couple’s social life and work. This means a long term impact on society because it affects family stability on one hand, and on the other hand treatment is often expensive and consumptive.

In vitro fertilization (IVF) often represents the ultimate step in our attempt to treat infertility. Nowadays this method is more and more used; couple’s expectations are higher and higher, so that optimizing the chance that one IVF pregnancy became a healthy newborn child is becoming an important issue (2, 3). One of the most important adverse outcomes attributed to IVF pregnancy is a high incidence of spontaneous abortion rate: 25 – 35% (4, 5).

In our attempt to understand and minimize the IVF pregnancy spontaneous abortion rate we analyzed the qualitative and quantitative impact of controlled ovarian hyperstimulation during IVF procedures.
Controlled ovarian hyperstimulation and IVF pregnancy prognosis

on pregnancy outcome, defined as the birth/abortion ratio.

MATERIAL AND METHODS

We studied 307 patients who had IVF fresh procedures in “Panait Sirbu” Clinical Hospital of Obstetrics and Gynecology, Bucharest - Department of Assisted Human Reproduction between 01.01.2008 – 31.12.2010 and obtained pregnancy; pregnancy rate according to our statistics is 34%. Patients were divided in 3 major groups according to the medication used for controlled ovarian hyperstimulation (recombinant follicle-stimulating hormone (FSH), highly purified urinary gonadotropin and the combination of the two drugs) and we analyzed the birth/abortion rate for all the 3 groups and the impact on the result obtained of a few variables: age, body mass index (BMI), endometrium thickness, number of oocytes retrieved, number of embryos obtained, number of days of stimulation and number of units of gonadotropin used for ovarian hyperstimulation per day. All patients had normal basal FSH and normal antral follicular count. All patients had long or short protocols for ovarian hyperstimulation. For statistic analysis we used the odd Student Test.

RESULTS

From the 307 patients who obtained pregnancy by IVF fresh procedures, 226 patients gave birth to one or more newborns (73.6%) and 81 patients suffered an abortion in the first or second trimester (26.4%) (fig. 1).

![Fig. 1. Pregnancy outcome after IVF fresh procedures](image)

Our first intention was to see if there is any difference between the group of patients whose pregnancies ended with birth and the group of patients whose pregnancies ended with abortion.

Student Test for patients’ age, for the patients whose pregnancies ended with birth (group A) towards those whose pregnancies ended with abortion (group B) is presented below (fig. 2.).

![Fig. 2. Student Test for patients’ age for patients who obtained pregnancies after IVF fresh procedures](image)
Average age for the patients who’s pregnancies ended with birth (group A = 33.3 years) is not statistically different from average age for the patients who’s pregnancies ended with abortion in the first or second trimester (group B = 33.4 years); $p > 0.1$ and $T = 0.31$.

Student Test for BMI, for the patients whose pregnancies ended with birth (group A) towards those whose pregnancies ended with abortion (group B) is presented below (fig. 3).

![Fig. 3. Student Test for patients’ BMI for patients who obtained pregnancies after IVF fresh procedures.](image)

Average BMI for the patients who’s pregnancies ended with birth (group A = 22.14 kg/m$^2$) is not statistically different from average BMI for the patients who’s pregnancies ended with abortion in the first or second trimester (group B = 22.7 kg/m$^2$); $p > 0.1$ and $T = 1.29$.

Student Test for endometrium thickness, for the patients who’s pregnancies ended with birth (group A) towards those who’s pregnancies ended with abortion (group B) is presented below (fig. 4).

![Fig. 4. Student Test for endometrium thickness for patients who obtained pregnancies after IVF fresh procedures.](image)

Average endometrium thickness for the patients who’s pregnancies ended with birth (group A = 11.8 mm) is not statistically different from average endometrium thickness for the patients who’s pregnancies ended with abortion in the first or second trimester (group B = 12.43); $p > 0.1$ and $T = 1.04$.

Student Test for the number of international units (IU) of gonadotropin used per day for ovarian hyperstimulation, for the patients who’s pregnancies ended with birth (group A) towards those who’s pregnancies ended with abortion (group B) is presented below (fig. 5).

Average number of units of gonadotropin used for ovarian hyperstimulation for the patients who’s pregnancies ended with birth (group A = 183.5 IU) is not statistically different from average number of units of gonadotropin used for the patients...
who’s pregnancies ended with abortion in the first or second trimester (group B = 201.0); p > 0.1 and T = 0.79.

Student Test for the number of days of hyperstimulation for the patients who’s pregnancies ended with birth (group A) towards those who’s pregnancies ended with abortion (group B) is presented below (fig. 6).

Fig. 5. Student Test for number of units of gonadotropin used for ovarian hyperstimulation for patients who obtained pregnancies after IVF fresh procedures.

Average number days of ovarian hyperstimulation for the patients who’s pregnancies ended with birth (group A = 11.3 days) is not statistically different from average number of days of ovarian hyperstimulation used for the patients who’s pregnancies ended with abortion in the first or second trimester (group B = 11.0 days); p > 0.1 and T = 0.46.

Student Test for the number of oocytes obtained from the patients who’s pregnancies ended with birth (group A) towards those who’s pregnancies ended with abortion (group B) is presented below (fig. 7).

Fig. 6. Student Test for number of days of ovarian hyperstimulation for patients who obtained pregnancies after IVF fresh procedures.

Fig. 7. Student Test for number of oocytes retrieved from patients who obtained pregnancies after IVF fresh procedures.
Average number of embryos from the patients whose pregnancies ended with birth (group A = 5.13) is not statistically different from average number of embryos obtained from the patients who’s pregnancies ended with abortion in the first or second trimester (group B = 4.9); p > 0.1 and T = 0.68.

Student Test for the common variables of the two groups (age, BMI, endometrium thickness, number of oocytes retrieved, number of embryos obtained, number of days of stimulation and number of international units of gonadotropin used per day) demonstrated that the average values of these variables are not significantly different.

Our next step was to divide the 307 group of patients according to the medication used for controlled ovarian hyperstimulation: 157 (51.1%) patients received recombinant FSH – group A, 42 (13.7%) patients received recombinant FSH and highly purified human gonadotropin – group B, 106 (34.5%) patients received highly purified human gonadotropin – group C, in 2 (0.7%) patients natural cycle was used – group D and in 1 (0.33%) patient we used a combination of clomiphene, highly purified human gonadotropin and recombinant FSH – E. (fig. 9).

We analyzed only the three groups of patients where the number of patients was good enough for the statistics (A, B and C). We calculated for each group the birth/abortion ratio and we considered the best ratio as the best pregnancy outcome.
For the group of patients who received recombinant FSH for ovarian hyperstimulation the birth/abortion rate was 3.24 (FSH group). For the group of patients who received highly purified human gonadotropin for ovarian hyperstimulation the birth/abortion rate was 2.31 (HPHG group) and for the group of patients who received both medications the birth/abortion rate was 2.73 (FSH + HPHG group). These data point out that the best ratio (3.24) was for the group of patients where recombinant FSH was used, followed by FSH + HPHG group (2.73), the worst result being registered for the HPHG group (2.31) (fig. 10).

![Fig. 10. Percentage distribution of pregnancies (birth and abortion) according to the medication used for ovarian hyperstimulation](image)

The next step was to determine if there is any favorable variable for this result. We used the odd Student Test to calculate the average value for all the variables considered (age, BMI, endometrium thickness, number of oocytes retrieved, number of embryos obtained, number of days of stimulation and number of units of gonadotropin used per day) for all the 3 groups of patients (FSH, HPHG and FSH+HPHG) (tab. 1).

**TABLE I**

Mean variables values according to the medication used for ovarian hyperstimulation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit of measure</th>
<th>FSH</th>
<th>HPHG</th>
<th>FSH + HPHG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Years</td>
<td>33.39</td>
<td>33.78</td>
<td>34.19</td>
</tr>
<tr>
<td>BMI</td>
<td>kg/ m$^2$</td>
<td>22.48</td>
<td>22.72</td>
<td>22.22</td>
</tr>
<tr>
<td>Endometrium thickness</td>
<td>mm</td>
<td>11.98</td>
<td>12.01</td>
<td>11.8</td>
</tr>
<tr>
<td>Number of oocytes retrieved</td>
<td></td>
<td>7.3</td>
<td>6.56</td>
<td>7.05</td>
</tr>
<tr>
<td>Number of days of stimulation</td>
<td></td>
<td>11.01</td>
<td>11.27</td>
<td>11.8</td>
</tr>
<tr>
<td>Number of embryos obtained</td>
<td></td>
<td>5.18</td>
<td>4.94</td>
<td>5.18</td>
</tr>
<tr>
<td>Number of units of gonadotropin/ day</td>
<td>IU</td>
<td>167.15</td>
<td>215.8</td>
<td>205.66</td>
</tr>
</tbody>
</table>

Student test for the variables: age, BMI, endometrium thickness, number of oocytes retrieved, number of days of stimulation and number of embryos obtained for the
patients in the FSH and HPHG groups indicated that the mean values of these variables are not statistically significantly different.

Student test for the variables: age, BMI, endometrium thickness, number of oocytes retrieved, number of days of stimulation and number of embryos obtained for the patients in the FSH and FSH+HPHG groups indicated that the mean values of these variables are not statistically significantly different.

Student test for the variables: age, BMI, endometrium thickness, number of oocytes retrieved, number of days of stimulation and number of embryos obtained for the patients in the HPHG and FSH+HPHG groups indicated that the mean values of these variables are not statistically significantly different.

Student test for the number of international units of gonadotropin used for ovarian hyperstimulation for the patients in the FSH group (group A) towards number of international units of gonadotropin used for ovarian hyperstimulation for the patients in the HPHG group (group B) is presented in fig. 11.

![Fig. 11. Student Test for the number of units of gonadotropin used for ovarian hyperstimulation for the patients in the FSH group towards patients in the HPHG group.](image1)

Average number of units of gonadotropin used for ovarian hyperstimulation in the FSH group (group A = 161.7 IU) is statistically significantly different from the average number of units of gonadotropin used for the HPHG group (group B = 215.8 IU) for p = 0.05.

Student test for the number of international units of gonadotropin used for ovarian hyperstimulation for the patients in the FSH group (group A) towards number of international units of gonadotropin used for ovarian hyperstimulation for the patients in the FSH+HPHG group (group B) is presented in figure 12.

![Fig. 12. Student Test for the number of units of gonadotropin used for ovarian hyperstimulation for the patients in the FSH group towards patients in the FSH+HPHG group.](image2)
Average number of units of gonadotropin used for ovarian hyperstimulation in the FSH group (group A = 161.7 IU) is statistically significantly different from the average number of units of gonadotropin used for the FSH+HPHG group (group B = 205.66 IU) for p = 0.05.

Student Test for the number of international units of gonadotropin used for ovarian hyperstimulation for the patients in the HPHG group (group A) towards number of international units of gonadotropin used for ovarian hyperstimulation for the patients in the FSH+HPHG group (group B) is presented in fig. 13.

Average number of units of gonadotropin used for ovarian hyperstimulation in the HPHG group (group A = 216.24 IU) is not statistically significantly different from the average number of units of gonadotropin used for the FSH+HPHG group (group B = 205.66 IU) for p >0.1.

**DISCUSSION**

The data presented above pointed out that apparently IVF pregnancy prognosis, defined as the best birth/abortion ratio is not dependent on variables such as: age, BMI, endometrium thickness, number of oocytes retrieved, number of days of stimulation, number of embryos obtained or number of units of gonadotropin used per day for ovarian hyperstimulation.

Still, when we analyzed the best birth/abortion ratio according to the medication used for ovarian hyperstimulation we could see that the best result was obtained when recombinant FSH was used. Different variables were analyzed and the number of units of gonadotropin used per day for ovarian hyperstimulation was found to be a favorable variable for a better IVF pregnancy outcome. Statistics pointed out that less the number of units of gonadotropin used per day, better the birth/abortion ratio for the patients where recombinant FSH was used (fig. 14).

Nowadays there are many attempts to identify any parameter that could improve IVF clinical outcome, defined as live birth rate or “baby taken home” rate. Regarding controlled ovarian hyperstimulation recent studies demonstrated the optimal number of oocytes to maximize the live birth rate (6), but few studies focused on the number of units of gonadotropin used per day. One of our previous small studies pointed out the possibility that less number of units of gonadotropin per day could mean better chances for a good pregnancy prognosis (7).
CONCLUSION
The best IVF pregnancy prognosis (the best birth/abortion ratio) was obtained when recombinant FSH was used. The majority of variables used in this study (age, BMI, endometrium thickness, number of oocytes retrieved, number of embryos obtained, number of days of ovarian hyperstimulation) are not favorable variables for this result, but the number of units of gonadotropin used per day for ovarian hyperstimulation seems to play an important role: less units of gonadotropin for the FSH group seems to be associated in our study group to a better birth/abortion rate.

We consider that our data gives an interesting perspective upon the connection between controlled ovarian hyperstimulation and pregnancy outcome, especially these days when tendencies are to obtain as many oocytes in one procedure as we can, which often means to use high doses of gonadotropin.

REFERENCES
2. Wilson CL, Fisher JR, Hammarberg K, et al. Looking downstream: a review of the literature on physical and psychosocial health outcomes in adolescents and young adults who were conceived by ART. *Hum Reprod* 2011; 26: 1209-1214.
Controlled ovarian hyperstimulation and IVF pregnancy prognosis


**NEWS**

**BREAST CANCER RISK AND LIPID METABOLISM GENES**

The breast cancer is an important pathology for women. The identification of biomarkers to highlight and differentiate between the estrogen receptor subtypes of breast cancer (sensitive or insensitive to hormones) would enable the adoption of prevention methods specific to each type of breast cancer. According to data published in Cancer Prevention Research, some genes related to lipid metabolism are related also with risk for hormone receptor-positive or hormone receptor-negative breast cancer. Khan and colleagues have analyzed by Illumina expression array and quantitative real-time PCR, the samples obtained by fine needle aspiration on the unaffected breast of women with unilateral breast cancer. The researchers identified 18 genes with high expression levels in samples from estrogen receptor-negative cases. They show that 4 genes (DHRS2, HMGCS2, HPGD and ACSL3) associated with lipid metabolism are a significant overexpression in estrogen receptor-negative cases. Another 2 genes (UGT2B11 and APOD) associated with lipid metabolism have a lower expression in estrogen receptor-positive cases. The results suggest that certain lipid metabolism genes may be potential biomarkers of different subtypes of breast cancer (Wang J, Scholtens D, Holko M, Ivancic D, Lee O, Hu H et all. Lipid metabolism genes in contralateral unaffected breast and estrogen receptor status of breast cancer. *Cancer Prev Res,* 2013; 6(4): 321–30).

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