Early pregnancy wastage: the role of repetitive human chorionic gonadotropin supplementation during the first 8 weeks of gestation

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Objective: To determine if repetitive administration of hCG causes decreased pregnancy wastage rates in patients who are at a high risk of luteal inadequacy.

Design: Ovulation induction using human menopausal gonadotropin (hMG)/human chorionic gonadotropin (hCG) or clomiphene citrate (CC) is associated with luteal phase defects that may cause increased pregnancy wastage. An increased risk of abortion exists also in pregnancies in patients with previous repeated miscarriage, women older than 37 years, and various causes of infertility such as hyperprolactinemia. Because the presumed common denominator to the increased rate of pregnancy wastage in all these cases is luteal dysfunction, repetitive hCG administration, 2,500 U two times weekly, was carried out between the 4th and 8th week of gestation in 249 cases of ovulation induction and/or previous abortions, whereas 198 gestations served as controls (no hCG administration).

Results: In the hCG treatment group, 43 ended in miscarriage (17.3%) versus 97 abortions in the control group (49%, P < 0.01). In 160 cases of hMG/hCG generated gestations, 94 received hCG and 66 did not. The pregnancy wastage rates were 21.3% and 42.4%, respectively (P < 0.05). In 144 cases of CC/hCG-induced pregnancies, 95 received hCG and 49 served as controls. The respective abortion rates were 15.8% and 44.8% (P < 0.01). The remaining 143 spontaneous conceptions occurred in infertile patients with previous repeated abortions. In 60 of these conceptions, hCG was administered during the first 4 weeks of gestation and 83 cases served as control. The pregnancy wastage rates were 13.3% versus 56.6%, respectively (P < 0.001).

Conclusion: Repetitive administration of hCG during the early gestation in cases that are at high risk of luteal inadequacy may significantly decrease the pregnancy wastage rate.

Key Words: Luteal support, pregnancy wastage, human chorionic gonadotropin supplementation, luteal inadequacy, habitual abortion, ovulation induction, infertility

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women 37 years of age or older who have required >6 months for conception. The spontaneous abortion rate among pregnancies resulting from gonadotropin induction of ovulation has been reported to be up to 28% after in vivo (6-9), and up to 33.6% after IVF and gamete intrafallopian transfer (7). Suggested associated factors include an increased multiple PR (6), severe ovarian hyperstimulation (6, 8), older age, and obesity (9).

The disappointment and stress caused by fetal loss in patients undergoing treatment for infertility make it important to analyze factors associated with various types of pregnancy wastage because preventive measures may be possible. A possible common denominator to the increased pregnancy wastage in cases of CC- and/or hMG-induced gestations, obesity, older age, and infertility may be luteal dysfunction (1). Because repetitive human chorionic gonadotropin (hCG) supplementation during the luteal phase was successful in increasing the PR and because the early gestation is dependent on the hormonal adequacy of the CL up to 8 weeks of gestation, we elected to examine the role of repetitive hCG administration during the first 4 weeks after recognition of pregnancy.

**MATERIALS AND METHODS**

Four hundred forty-seven pregnancies in 381 infertile patients were divided between the treatment or control group during the last 5 years. Each pregnant patient in whom the pregnancy was either generated by ovulation induction (hMG/hCG or CC/hCG) or the patient has suffered from previous recurrent abortions was randomized to either receive repetitive hCG (treatment group) or not to receive hCG injections (control group). In the treatment group, each patient received an intramuscular injection of 2,500 U of hCG (Chorigon; Teva Pharmaceutical Ind. Ltd., Petah-Tikva, Israel) two times weekly, from the diagnosis of pregnancy until the 8th week of gestation. The mean number of ampules per patient was 7 (range 6 to 8). The diagnosis of pregnancy was made by either identification of an intrauterine gestational sac by transvaginal sonography or by rising β-hCG concentrations, 2 days apart, when no hCG was administered between the two blood tests. The control group did not receive any treatment. Patient’s age, weight, and height, as well as the number of previous abortions were not significantly different between the treatment and control groups. Each patient was supplied with the information of the possibility of an increased rate of miscarriage in infertile patients and was given the option to be either in the control or in the treatment group. In cases in which the patient was indifferent, the inclusion in the control or treatment group was prospectively randomized. Sixty-one patients elected to be in the treatment group, and 18 patients decided not to receive hCG injections (control group) (Table 1). The remaining 368 gestations were randomized between the treatment (188 cases) or control group (180 cases) (Table 1). Of the 447 pregnancies, 249 were treated with hCG injections two times weekly (treatment group), and 198 gestations did not receive hCG (control group). Of the 447 pregnancies, 160 were generated by hMG/hCG and 144 by CC/hCG ovulation induction, whereas 143 were spontaneous pregnancies in patients with previous repeated abortions.

**RESULTS**

Of the overall 249 gestations in the treatment group, 43 ended in miscarriage (17.3%), whereas 97 of the 198 pregnancies in the control group ended
in first trimester abortions (49%) (Fig. 1A). Of the 160 gestations that were generated by hMG/hCG, repetitive hCG injections were administered in 94 (treatment group), whereas 66 comprised the control group. The pregnancy wastage rate was 21.3% (20/94) in the treatment group versus 42.4% (28/66) in the control group ($P < 0.05$, $\chi^2$ test) (Fig. 1B).

In the 144 gestations generated by CC or CC/hCG ovulation induction, 95 comprised the treatment group and 49 the control group. In the treatment group, the abortion rate was 15.8% (15/95), whereas in the control group it was 44.8% (22/49) ($P < 0.01$, $\chi^2$ test) (Fig. 1C). Eight of the 60 spontaneous pregnancies in infertile patients who were treated by repetitive hCG injections during the 2nd month of gestation (weeks 5 to 8) ended in early miscarriage (13.3%), whereas 47 of the 83 pregnancies in the respective control group ended in first trimester abortions (56.6%), ($P < 0.001$, $\chi^2$ test), (Table 2) (Fig. 1D). There was no significant difference in pregnancy wastage rate between those patients who decided whether or not to receive hCG injections and those in the respective randomized treatment or control groups (Table 1).

**DISCUSSION**

Superovulation and ovulation induction create a spectrum of hormonal alterations with subsequent critical effects in terms of implantation and maintenance of pregnancy (10). Inadequate or deficient CL function is the principal factor in 3.5% to 4% of unselected infertile couples (1, 11), but its incidence is higher in women with a history of recurrent abortion and is diagnosed more frequently in patients undergoing ovulation induction by CC or hMG/hCG (1, 11, 12), hyperprolactinemic patients, and patients with unexplained infertility (11). Luteal dysfunction

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**Figure 1** Pregnancy wastage rates in all patients who received hCG two times weekly between the 5th and 8th week of gestation and in the control (A). Pregnancy wastage rates in the group of pregnant patients who conceived after hMG/hCG ovulation induction and were treated with hCG two times a week and in their respective controls (B). Pregnancy wastage in pregnancies generated by CC or CC/hCG ovulation induction who received hCG injections and in their controls (C). Pregnancy wastage rates in spontaneous pregnancies in a group of patients with previous abortions who were treated with hCG injections two times a week during the 2nd month of gestation and in their controls (D).
Table 2 Pregnancy Wastage in Pregnancies Treated or Untreated by Repetitive HCG Injections During the 2nd Month of Gestation

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>hCG (+)</th>
<th>Control group</th>
<th>hCG (-)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Abortions</td>
<td>Pregnancy wastage</td>
<td>No. Abortions</td>
<td>Pregnancy wastage</td>
<td>Probability</td>
</tr>
<tr>
<td>HMG/hCG</td>
<td>94</td>
<td>20</td>
<td>66</td>
<td>28</td>
</tr>
<tr>
<td>CC or CC/hCG</td>
<td>95</td>
<td>15</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>60</td>
<td>8</td>
<td>83</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>249</td>
<td>43</td>
<td>198</td>
<td>97</td>
</tr>
</tbody>
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can also cause recurrent early abortions, often occurring before the patient realizes she is pregnant (1, 13, 14).

Because the function of the CL is crucial during the first 7 to 9 weeks of pregnancy, luteectomy early in pregnancy can precipitate abortion (15), and because early pregnancy loss in primates can be induced by injections of anti-hCG serum (16), we decided to examine the hypothesis that repetitive hCG administration would rescue those gestations that might have been aborted because of inadequate CL function. The prevalence of inadequate luteal phase in patients with recurrent abortions was found to range from 23% to 38% (17-20). Harrison (21) found an increased salvage in women with a history of habitual abortion when they were treated with hCG. The salvage rate was excellent (100%) in the hCG group (10 of 10) and very poor (30%) in the placebo group (3 of 10). Although the difference is apparently convincing, this study (21) consisted of only 20 patients. Therefore we have decided, about the time this study was published, to assess the value of hCG administration in early gestation in a large group of patients who may be at high risk of luteal dysfunction. Indeed, although our study does not contain a placebo-treated group, the difference between the treatment and control groups, in terms of pregnancy wastage, is significant (17.3% versus 49% pregnancy wastage, respectively).

The randomization was carried out by alternating every new pregnancy to either the treatment or control group. However, not to violate the patients' right for free decision, the information concerning the goal of the study was supplied to the patients and those who wanted to be included in a specific group were free to do so. Apparently, the means on which each individual patient was included in the treatment (hCG administration) or control (no hCG) group did not influence the pregnancy wastage rate. There was no significant difference between the pregnancy wastage in those cases who were treated by hCG because of their free decision (18%) or by randomization (17.5%), or between the respective control groups (61% and 47.8%) (Table 1). The bias caused by the fact that 18% of our cases (79/447) were not randomized does not seem to influence the results. Therefore we could combine all the treated or untreated cases in each subgroup (Table 2) without changing the results.

According to the classic study of Hertig et al. (22), published >30 years ago, it appears that 56% of the conceptions would not proceed beyond the early stage of pregnancy (7). More recently Wilcox et al. (23), who used a very sensitive immunoradiometric assay for hCG, identified 198 pregnancies near the expected time of implantation. Of these, 43 (22%) ended before and 19 (9%) aborted after the clinical detection of pregnancy (7, 23). The total pregnancy loss was 31% (23), a figure that corresponds well with the estimation by Hertig et al. (22) and with our results of 42.4% to 56.6% early pregnancy wastage in the ovulation induction or spontaneous control groups, respectively. Moreover, Boklage (5) has recently calculated the survival probability of human conceptions and found that at least 73% of spontaneous single conceptions have no real chance of surviving 6 weeks of gestation. Of the remainder, approximately 90% will survive to term (5). Because in our study the patients were detected very early in pregnancy, it is not surprising that the pregnancy wastage in the hCG untreated (control) group is so high (49%). The difference between the hCG-treated and -untreated groups is significant in the hMG/hCG and CC/hCG ovulation induction groups, in which a high incidence of luteal dysfunction is documented (1, 6, 7, 11) but also in a group of infertile patients with previous abortions (18-21). The mechanism of the beneficial effect of hCG administration is unknown, but because it was common to all three treatment groups in our study, we suggest...
that the common denominator to the increased pregnancy wastage rate in infertile patients may indeed be CL inadequacy and that in a significant proportion of the achieved pregnancies it may be curable.

The role of hCG administration in rescue of a deficient CL is understandable in those cases in which the endogenous rise in hCG concentrations may be several days late. However, such an effect is less understandable for those cases with endogenous hCG concentrations > 250 to 500 U/L because administration of 2,500 U of hCG to a nonpregnant patient will generate hCG concentrations at approximately this range. In this case, one of two theoretical explanations may be suggested: (1) the endogenous hCG may be of a low bioactivity, therefore incapable of adequately stimulating the CL to secrete normal amounts of sex steroids and growth factors (such as relaxin, inhibin, activin) or (2) the commercially administered hCG is manufactured from human pooled pregnant urine, therefore containing also substances with immunomodulatory influence. Of course, both these suggested explanatory mechanisms are theoretical and await validation. Until then, we can only conclude that empirical treatment with repetitive hCG administration between the 5th and 8th week of gestation is effective in decreasing pregnancy wastage in cases of ovulation induction, repeated previous miscarriages, and luteal inadequacy.

REFERENCES