Day 14 maternal serum progesterone levels predict pregnancy outcome in IVF/ICSI treatment cycles: a prospective study

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BACKGROUND: Serum progesterone has been advocated as a tool in the diagnosis of early pregnancy failure. We conducted this prospective study in order to investigate the potential value of early (14 days after oocyte recovery) serum progesterone measurement, in women undergoing IVF/ICSI and receiving rectal progesterone supplements, in relation to pregnancy outcome. METHODS: 442 women consecutively treated by IVF or ICSI had serum progesterone and bhCG levels prospectively measured 14 days after oocyte retrieval (day 0). All women received natural progesterone 400 mg rectally until the pregnancy test on day 14. Pregnant women were followed up by serial transvaginal ultrasound scans to 8 weeks gestation. RESULTS: 115 women (26%) had a viable intra-uterine pregnancy at 8 weeks gestation, 80 (18.1%) had an abnormal pregnancy (biochemical, ectopic, miscarriage) and 247 (55.9%) failed to conceive. Women with on-going pregnancies had significantly higher serum progesterone levels (median: 430, 95%CI: 390–500 nmol/l) compared to those who had either an abnormal pregnancy (72, 48–96 nmol/l; \(P<0.001\)) or failed to conceive (33, 28–37 nmol/l; \(P<0.001\)). Receiver-operator curve analysis demonstrated that a single serum progesterone on day 14 post-oocyte retrieval, could highly differentiate between normal and abnormal pregnancies (area under the curve \(= 0.927, 95\%\)CI \(= 0.89–0.96\); \(P<0.0001\)). CONCLUSIONS: In spite of exogenous progesterone supplementation, serum progesterone levels, from as early as 4 weeks gestation (day 14 post-oocyte retrieval) were significantly elevated and predicted women destined to have viable intra-uterine pregnancies. These high levels are suggestive that endogenous progesterone is already sufficient in viable pregnancies and that exogenous progesterone administration will not rescue a pregnancy destined to result in a miscarriage. Single serum progesterone measurement could be a useful indicator of pregnancy outcome in women undergoing IVF or ICSI treatment.

Key words: bhCG/early pregnancy/IVF/progesterone/prognosis

Introduction

Controlled ovarian hyperstimulation (COH) protocols for in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) are stressful, invasive and can be associated with adverse pregnancy outcome, including miscarriage and ectopic pregnancy. The early prediction of pregnancy outcome has therefore great importance for both couples and medical practitioners on IVF units.

Progesterone dynamics in early pregnancy have been studied at length, and it is primarily luteal phase progesterone that maintains the developing trophoblast for the first 7 to 8 weeks of gestation (Norman et al., 1988; Khan-Dawood et al., 1989). There are reports that luteal and placental progesterone production may be defective for days or weeks before an abnormal pregnancy is diagnosed. As a result, measurement of serum progesterone has been advocated as an early means of detecting abnormal pregnancies (Yeko et al., 1987; Hahlin et al., 1990). More recent evidence suggests that serum progesterone measured in early pregnancy is the most powerful single predictor of pregnancy outcome in natural conceptions (Daily et al., 1994; Leduc et al., 1994; Al-Sebai et al., 1995; Elson et al., 2003). Discriminatory progesterone levels ranged from 21.4 to 82.5 nmol/l for predicting abnormal or normal gestations, respectively (Yeko et al., 1987; Buck et al., 1988; Stovall et al., 1989; Peterson et al., 1992; Elson et al., 2003). Overall, a level of \(>66\) nmol/l could be reassuring of a normal outcome, whereas those \(<40\) nmol/l are likely to be associated with abnormal pregnancies (Mol et al., 1998).

Those findings have been derived from spontaneous pregnancies and cannot be extrapolated to IVF/ICSI cycles, as it is unclear what the influence is of GnRH agonist or antagonist treatment in the production of progesterone from corpus luteum. Moreover, it is unclear what the effect of multiple corpora lutea (produced during COH) is on serum progesterone values. It is possible that multiple corpora lutea lead to
higher serum progesterone levels even with a non-viable pregnancy. Lastly, exogenous progesterone luteal support may significantly affect the potential efficacy of serum progesterone to predict the outcome of the cycle (Isaacs et al., 1994; O’Leary et al., 1996).

Few studies have attempted to use serum progesterone testing to predict outcome in IVF/ICSI cycles and none has produced convincing conclusions, whether because of the wide range of treatment cycles included (COH, frozen embryo replacement cycles, ovulation induction) (Shulman et al., 1994; Al-Ramahi et al., 1999; Homan et al., 2000), or retrospective analysis used (Shulman et al., 1994; Al-Ramahi et al., 1999; Homan et al., 2000), or poor specification of the timing of the progesterone test (Al-Ramahi et al., 1999; Homan et al., 2000), or inadequate ultrasound follow up (Yamashita et al., 1989; Shulman et al., 1994; Homan et al., 2000). Furthermore, in studying women undergoing IVF/ICSI with exogenous progesterone support, it is essential to use non-pregnant women as controls to account for pharmacological effects on progesterone levels (Bustillo et al., 1993; Vicdan and Zeki Isik, 2001).

This prospective study was designed to investigate the potential value of early (14 days after oocyte recovery) serum progesterone measurement in women undergoing IVF/ICSI and receiving rectal progesterone supplements. The study has also examined whether a day 14 progesterone test can predict pregnancy outcome. In the design of this study a conscious effort was made to avoid the shortcomings of previous studies. We recruited a well-selected homogeneous population, who underwent similar superovulation protocols, received the same dose of exogenous progesterone and were followed up prospectively by ultrasound.

Materials and methods

Subjects

The study was approved by the Research Ethics Committee of Hammersmith Hospital. All women in this study were treated by IVF or ICSI at the IVF unit in Hammersmith Hospital. Consecutive women starting IVF/ICSI cycles were enrolled in a prospective study between May and December 2003. Only those who completed the IVF/ICSI–Embryo Transfer (ET) cycle and had a pregnancy test in our laboratory 14 days post-oocyte retrieval were included. Women who had a blood test either in another laboratory or on a different day apart from day 14, or were lost on follow up, were excluded.

Two standard superovulation protocols were used. In the gonadotrophin releasing hormone (GnRH) agonist protocol, women began down regulation with buserelin acetate (Shire Pharmaceuticals, Andover, UK) on day 2 or 21 of their cycles for 2 weeks, following which they started ovarian stimulation with recombinant follicle stimulating hormone (rFSH) (Puregon, Organon, UK or Gonal-F, Serono, UK). In the GnRH antagonist protocol women began with rFSH injections first and added the GnRH antagonist Ganirelix (Orgalutran, Organon, UK) or Cetrorelix (Cetrodote, Serono, UK) when at least one leading follicle reached 14 mm in size. In both protocols there was close monitoring of the ovarian response with transvaginal ultrasonography and serum estradiol and luteinizing hormone (LH) measurements. When at least three follicles >17 mm in size, women were administered 10.000IU of human chorionic gonadotrophin (Pregnyl, Organon, UK or Profasi, Serono, UK) to simulate the LH surge of a natural cycle. They underwent transvaginal ultrasound-guided oocyte recovery (TVOR) 36 h later, under intravenous sedation. That day was defined as day 0. All women were given a 7-day course of doxycycline afterwards. Oocytes were fertilized in vitro by conventional IVF or single sperm injection (ICSI), and a maximum three embryos were transferred in the uterine cavity 2 or 3 days afterwards. After ET, all women had luteal phase support with natural progesterone, given as a single injection 100mg (Gestone, Ferring, UK) on the day of ET and then daily 400mg in the form of a single rectal suppository (Cyclogest 400, Shire Pharmaceuticals, UK) until their pregnancy blood test on day 14 post-TVOR.

Women who, on day 14, had levels of the bhCG <1IU/l were discharged. The rest were followed up either with further blood tests until bhCG was <1IU/l, or with serial transvaginal ultrasonography, until 8 weeks of gestation when they had a normal pregnancy, or until they were diagnosed with a miscarriage or an ectopic pregnancy.

Three groups of women were defined according to pregnancy outcome: non-pregnant; women with abnormal pregnancy (biochemical, miscarriage or ectopic); and women with viable intra-uterine pregnancy (singleton, twin or triplet).

Hormone assays

Blood samples were drawn on day 14 between 7 and 9 am, in standard SST gel tubes (Becton Dickinson, Plymouth, UK) and were allowed to clot before centrifugation at 3000 g for 10 min in order to separate the serum. Samples were transferred to the laboratory within 1 h of collection and analysed on the same day for progesterone with sequential competitive immunoassay (Immulite, DPC, Los Angeles, CA) and bhCG with microparticle immunoassay (Architect, Abbott laboratories, Illinois, IL). The analytical performance characteristics of the progesterone assay were: sensitivity 0.6nmol/l, inter-assay precision (coefficient of variation CV) 6.8% at 24nmol/l and 9% at 55nmol/l; while for bhCG they were: 0.1IU/l, 4.5% at 35IU/l and 4.1% at 89IU/l, respectively. The progesterone results were given to the investigators at the end of the study.

Statistical analysis

Data were analysed on GraphPad Prism software (San Diego, California, CA). A P-value <0.05 was considered statistically significant. Nonparametric data between the three groups were compared with Kruskal–Wallis test followed by Dunn’s post-hoc analysis. One-way analysis of variance (ANOVA) was used to compare differences for all the parametric values.

To examine the value of serum progesterone testing in distinguishing ongoing pregnancies from those destined for failure (biochemical, miscarriage, ectopic) we used receiver operating characteristic (ROC) analysis. The ROC curve plots the relationship between sensitivity and false-positive rate at varying progesterone concentrations. The suggested cut-off levels for predicting viability was derived from the ROC curve. Sensitivity, specificity and positive or negative predictive value was calculated for each cut-off level of progesterone.

Spearman correlation test (non-parametric) was used to correlate progesterone and bhCG values and correlation coefficient (r) along with its confidence intervals (95%CI) was calculated.

Results

Five hundred and thirteen women completed an IVF/ICSI–ET cycle during the study period. Among these, a total of
442 women were included in the study, as 71 did not meet with the inclusion criteria either because they had their blood test performed on a date different than day 14 \((n = 14)\), or performed in a different laboratory \((n = 49)\), or were lost on follow-up \((n = 8)\). The clinical pregnancy rate in this group was 31.5% per embryo transfer.

One hundred and fifteen women \((26\%)\) had a viable intra-uterine pregnancy at 8 weeks gestation, 80 \((18.1\%)\) had an abnormal pregnancy \((biochemical, ectopic, miscarriage)\) and 247 \((55.9\%)\) failed to conceive.

Table I shows that women with ongoing pregnancies were significantly younger compared with women with abnormal pregnancy or those who were non-pregnant and received significantly lower treatment doses of rFSH. There were no significant differences in the number of days of stimulation, endometrial thickness or peak serum estradiol.

Serum progesterone and bhCG concentrations in each group and subgroup 14 days after TVOR according to outcome are summarized in Table II. Women with viable pregnancy or those who were non-pregnant and received significantly higher serum progesterone \((median: 430 \text{ nmol/l})\) and bhCG \((median: 150 \text{ IU/l})\) or failed to conceive. The use of a GnRH agonist or antagonist protocol did not alter these results, as serum progesterone remained significantly higher in women with viable intra-uterine pregnancies compared with those who received the same treatment protocol and had either an abnormal pregnancy or failed to conceive (Table III). There was no significant difference in progesterone levels between women that followed a GnRH agonist or antagonist protocol and had the same pregnancy outcome.

Women with viable pregnancies produced significantly more oocytes than non-pregnant women \((11 vs 9; P < 0.01)\), but did not differ compared to women with abnormal pregnancy \((11 vs 10; P = 0.3, \text{NS})\) (Table I). There was no correlation between the number of oocytes collected and the levels of serum progesterone, irrespective of pregnancy outcome \((r = 0.09; P = 0.6, \text{NS})\).

Investigation of the relation between serum progesterone and bhCG concentrations both in normal and abnormal pregnancies showed a strong correlation between progesterone and bhCG only in abnormal pregnancies \((r = 0.52; P < 0.001)\) but not in viable intra-uterine pregnancies \((r = 0.02; P = 0.8, \text{NS})\).

Using receiver-operating characteristics (ROC) analysis, the ability of day 14 serum progesterone to differentiate between normal and abnormal pregnancies is high \((area under the curve = 0.927; 95\% \text{ CI} = 0.892–0.962; P < 0.0001; \text{Figure 1})\).

The predicted probability of a pregnancy being viable intra-uterine for any given progesterone concentration plotted together with the sensitivity and specificity is presented in Figure 2. Sensitivity and specificity curves meet at a serum progesterone level of 103 nmol/l. This progesterone level gives a probability for the detection of women who will have a viable intra-uterine pregnancy of 88.2%, with a sensitivity and specificity of 84%.

**Discussion**

This study has assessed the potential value of early serum progesterone measurement in women undergoing IVF/ICSI

### Table I. Patients' profile and treatment details

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subgroup</th>
<th>n</th>
<th>Percentage (%)</th>
<th>Progesterone (median)</th>
<th>95% CI</th>
<th>bhCG (median)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Not pregnant</td>
<td>247</td>
<td>55.9</td>
<td></td>
<td>33^</td>
<td>28–37</td>
<td>N/A</td>
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<tr>
<td>Abnormal pregnancy</td>
<td>80</td>
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<td></td>
<td>72^</td>
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<td>miscarriage</td>
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<td>3.6</td>
<td></td>
<td>160</td>
<td>100–300</td>
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<td>58–120</td>
</tr>
<tr>
<td>ectopic</td>
<td>8</td>
<td>1.8</td>
<td></td>
<td>34</td>
<td>8.7–75</td>
<td>29</td>
<td>9.8–55</td>
</tr>
<tr>
<td>biochemical</td>
<td>56</td>
<td>12.7</td>
<td></td>
<td>31</td>
<td>28–52</td>
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<tr>
<td>Viable pregnancy</td>
<td>115</td>
<td>26.0</td>
<td></td>
<td>430^</td>
<td>390–500</td>
<td>150^</td>
<td>130–180</td>
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\(^{\^}\)P < 0.001, viable pregnancy vs abnormal pregnancy vs not pregnant.

\(\times \)P < 0.05, viable pregnancy vs not pregnant.

+ NS.

### Table II. Serum progesterone (nmol/l) and bhCG (IU/l) concentrations collected 14 days post-oocyte recovery according to outcome

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\(^{\^}\)P < 0.001, viable pregnancy vs not pregnant.
and receiving rectal progesterone supplements. In spite of exogenous progesterone supplementation, serum progesterone levels were significantly elevated, from as early as 4 weeks gestation, in women destined to have viable intra-uterine pregnancies. It has also been demonstrated that women who failed to conceive had very low serum progesterone levels at this date despite exogenous supplementation. Women with an abnormal pregnancy had significantly higher serum progesterone levels compared with those who were not pregnant.

The vast majority of IVF practitioners have employed in their superovulation protocols luteal supplementation with progesterone, in order to compensate a possible iatrogenic luteal phase defect (Macklon and Fauser, 2000). This has been used both in GnRH agonist and antagonist protocols. GnRH agonists cause suppression of pituitary LH secretion for as long as 2 to 3 weeks after the last dose of agonist (Sungurtekin and Jansen 1995; Beckers et al. 2000). Without this LH signal, the corpus luteum may be dysfunctional, and subsequent progesterone secretion may be abnormal, which could lead to decreased implantation and decreased pregnancy rates. In contrast, the recovery of pituitary LH release is almost immediate after the cessation of GnRH antagonist administration (Beckers et al., 2003). Recent evidence has suggested that luteal phase is insufficient in ovarian stimulation protocols with the use of GnRH antagonist, due to the supraphysiological steroid levels in the late follicular and early luteal phase, which are both related to the number of developing follicles and subsequent corpora lutea (Tavaniotou et al., 2002; Beckers et al., 2003).

Different doses, durations and types of luteal phase support are used, but the best dose, duration or type of treatment remains controversial. In a large meta-analysis, Pritts and Atwood (2002) have demonstrated that the need for progesterone luteal supplementation is real, conferring benefit to fertility in women undergoing IVF cycles. The optimal length of treatment remains unsolved at present, and further trials will be needed before clear recommendations can be made.

Although serum progesterone has been advocated to be the single most powerful predictor of pregnancy outcome in spontaneous conceptions (Elson et al., 2003), there is very conflicting evidence when this is tested in COH protocols that use progesterone luteal support. These women will have

| Table III. Serum progesterone concentrations (nmol/l) according to superovulation protocol used (GnRH agonist or antagonist) and outcome |
|-----------------------------|-----------------------------|-----------------------------|
| Outcome                  | GnRH agonist |              | GnRH antagonist |              |
|                           |   n         | Progesterone (median) | 95% CI         |   n         | Progesterone (median) | 95% CI         |
| Not pregnant              |  95        | 33<sup>a</sup>       | 25–38          |  152      | 34<sup>b</sup>       | 29–42          |
| Abnormal pregnancy        |  41        | 69<sup>c</sup>       | 45–101         |  39       | 73<sup>d</sup>       | 42–110         |
| Viable pregnancy          |  76        | 440<sup>e</sup><sup>f</sup> | 390–520       |  39       | 430<sup>e</sup><sup>f</sup> | 350–550       |

<sup>a</sup> P < 0.001, viable pregnancy vs not pregnant (GnRH agonist protocol).
<sup>b</sup> P < 0.001, viable pregnancy vs abnormal pregnancy (GnRH agonist protocol).
<sup>c</sup> P < 0.001, viable pregnancy vs not pregnant (GnRH antagonist protocol).
<sup>d</sup> P < 0.001, viable pregnancy vs abnormal pregnancy (GnRH antagonist protocol).

There is no significant difference between women that followed a GnRH agonist or antagonist protocol and had the same pregnancy outcome.

Figure 1. Receiver-operating characteristics (ROC) curve demonstrating the ability of serum progesterone concentration to predict pregnancy viability as early as 14 days post-oocyte retrieval in IVF/ICSI cycles that use progesterone luteal support. The diagnostic accuracy for differentiating between normal and abnormal pregnancies (area under the curve) is 0.927 (95% CI = 0.892–0.962; P < 0.0001).

Figure 2. Predicted probability of a pregnancy being viable intra-uterine for any given progesterone concentration plotted together with the sensitivity and specificity. Sensitivity and specificity curves meet at a serum progesterone level of 103 nmol/l. That progesterone level gives a probability for the detection of women that will have a viable intra-uterine pregnancy of 88.2% with a sensitivity and specificity of 84%.
multi-follicular development, so if pregnancy occurs there will be multiple corpora lutea. Furthermore, in the superovulation protocols that involve progesterone luteal support it might be expected that, if these women conceive, they would have higher levels of serum progesterone compared with the levels found in a spontaneous pregnancy. This might lead to yet higher levels of serum progesterone, even with an abnormal non-viable pregnancy.

Lower and Yovich (1992) reported that the discriminatory capacity of serum progesterone measurement increases with gestational age in a population including spontaneous and assisted conception pregnancies. Vicdan and Zeki Isik, (2001) concluded that there was no difference between progesterone levels on day 11 post-oocyte retrieval, while Al-Ramahi et al. (1999) suggested that a serum progesterone level of <45 nmol/l in early pregnancy can predict non-viable pregnancy after COH. Shulman et al. (1994) reported that only at day 10 post-embryo transfer did those patients with ectopic pregnancy show lower serum progesterone compared with patients with intra-uterine pregnancy (all women received hCG luteal support). None of these studies used, as controls, women who failed to conceive and received progesterone luteal support.

The present study was prospective and specifically investigated women undergoing COH for IVF/ICSI who received similar exogenous natural progesterone. As a predictive of pregnancy outcome, a day-14 serum progesterone test in this group of women was found to have a good discriminatory capacity to differentiate between normal and abnormal outcome. It was shown that this discriminatory capacity of progesterone testing was not affected by the treatment protocol used (GnRH agonist or antagonist). These results are in agreement with the evidence available for spontaneous conceptions (Elson et al., 2003), leading to the suggestion that exogenous progesterone supplementation did not affect the diagnostic ability of the test.

Trying to investigate the relation between bhCG and progesterone concentrations both in normal/ongoing and abnormal/destined-to-fail pregnancies it was found that there was a strong correlation between bhCG and progesterone only in abnormal pregnancies. The main drive for progesterone production comes from continuing stimulation of the corpora lutea by hCG. It seems that in abnormal pregnancies, the low progesterone values can be explained by the lower bhCG concentrations found, and most likely there is no other independent determining factor.

The high progesterone levels found at day 14 in normal pregnancies indicate that endogenous progesterone in viable pregnancies is already sufficient to compensate a possible iatrogenic luteal phase defect caused by the use of GnRH agonists or antagonists. That raises the question about the value of giving additional progesterone after day 14 in early pregnancy. This practice, even though hardly supported by evidence in the literature, is still commonly performed. Previous studies have suggested discriminatory progesterone levels from 21.4 to 82.5 nmol/l for predicting abnormal or normal gestations, respectively (Yeko et al., 1987; Buck et al., 1988; Stovall et al., 1989; Peterson et al., 1992; Elson et al., 2003). In this study we found that a progesterone level at day 14 of 103 nmol/l gives a probability for the detection of women that will have a viable intra-uterine pregnancy of 88.2% with a sensitivity and specificity of 84%.

It should be emphasized that we found a considerable overlap in progesterone values between women that will have either a normal or abnormal pregnancy outcome from day 14, which needs to be taken into account if the test is going to be used to predict pregnancy outcome. Serum progesterone testing in early pregnancy has been used by clinicians mostly as a tool to identify patients at risk of ectopic pregnancy. In the present study progesterone levels at day 14 in women with ectopic pregnancy were persistently low (median: 34, 95%CI: 8.7–75). Due to the small number of women with ectopic pregnancies found (n = 8), we were unable to use ROC analysis to determine if progesterone testing from early as day 14 would be useful to identify the sub-group of women that will have an ectopic pregnancy.

In conclusion, in spite of exogenous progesterone supplementation, serum progesterone levels were significantly elevated, from as early as 4 weeks gestation, in women destined to have viable intra-uterine pregnancies after superovulation for IVF/ICSI. Single serum progesterone measurement could be used as an indicator of pregnancy viability. This may reduce anxiety for patients and assist the clinician in early pregnancy monitoring and management. Larger studies are needed, to investigate whether serum progesterone could be used as a prognostic test to predict which women will have an ectopic pregnancy following a superovulation protocol.

Acknowledgements

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Conflict of interest

Mr G.Trew is a shareholder and adviser of Shire pharmaceutical. Hammersmith IVF unit has received research support from Alpharma for a separate progesterone study.

References


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