

Letters-to-the-editor

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Uterine Receptivity in Subjects With Ovarian Failure

To the Editor:

I read with interest the excellent manuscript by de Ziegler and Frydman¹ in which they demonstrated a much higher pregnancy rate from the transfer of cryopreserved-thawed embryos originating from prior donor oocyte cycles as compared with those originating from regular in vitro fertilization (IVF) cycles. Their study tends to refute the commonly believed hypothesis that the hyperstimulation regimen per se may have a negative influence on the success of a given IVF-embryo transfer cycle. Because donor oocytes are generally obtained from a group of fertile women, the de Ziegler and Frydman data could certainly be used to support the following conclusion: the reason that almost all IVF centers with donor oocyte programs have much higher pregnancy rates from embryos originating from donors rather than from their regular IVF cycles^{2,3} is related to better quality oocytes from the donors. Indeed this was suggested by them.

They also proposed a second mechanism which was quite provocative. Speculating that since human chorionic gonadotropin/luteinizing hormone (hCG/LH) receptors have been found in human uteri, they hypothesized that the tonic high serum gonadotropin levels in ovarian failure patients might in some way positively influence endometrial receptivity.

The major source of our donor oocytes come from patients who are, themselves, having IVF but are willing to share half of their oocytes in exchange for sharing costs. We presented our data at the 46th Annual Meeting of The American Fertility Society,⁴ in which donors shared oocytes with 22 recipients in 38 cycles. Despite equal numbers of embryos

transferred (2.7 embryos for donors, 2.8 embryos for recipients), there was a much higher pregnancy rate in the recipients (11 of 38 or 28.9%, with only 1 spontaneous abortion) compared with the donors (only 4 of 38 or 10.5%, 1 spontaneous abortion). We proposed as one mechanism that the hyperstimulation regimen was a negative factor (and the title reflected this). However, an alternate suggested was the increased uterine receptivity in the recipients, which we attributed possibly to the supplemental estrogen taken by the recipients in the luteal phase. Expanding the data to 92 matched cycles, a higher pregnancy rate per cycle was still maintained in the recipients (17 pregnancies, 18%) versus 9 in the donors (9 pregnancies, 10%) ($P = 0.01$; χ^2 analysis). Of 248 donor embryos transferred, only 5 (2%) survived to the last trimester compared with 13 of 257 (5%) recipient embryos who survived to the same length of time ($P = 0.02$; Fisher's Exact Test).

Thus, our data lends support to the hypothesized mechanism of increased uterine receptivity possibly related to increased receptors from high gonadotropin levels in patients with ovarian failure. Because de Ziegler and Frydman used the same luteal phase support in donors and recipients, the mechanism that we proposed of the estrogen improving receptivity no longer seems tenable.

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Reply of the Authors:

We thank Dr. Check for his interest in our article.¹ The data that Dr. Check presented at the 46th Annual Meeting of The American Fertility Society² after our own paper was completed brings an original new insight to the puzzling difference in endometrium receptivity observed between recipients of oocyte donation and regular in vitro fertilization (IVF) patients.^{3,4} The originality of Check's model lies in a unitary source of oocytes. In his program, oocytes were donated by IVF patients wishing to share the medical cost of their IVF procedure with a matched recipient. Oocytes retrieved from the IVF patient are therefore equally divided between the patient and a woman deprived of ovarian function receiving hormonal substitution to prepare for endometrium receptivity. This approach is a truly ingenious way to solve the clinical problem of finding a reliable, ethically acceptable source of anonymously donated oocytes. Moreover, it is very interesting that, using this original model, Check's group also observed the higher pregnancy rate described by others in recipients of oocyte donation.^{3,4} This information is a strong argument to suggest that the difference in pregnancy rate observed between egg donation and regular IVF programs might, at least in part, not be due to a difference in oocyte quality. The approach selected by our group to find an acceptable source of donated oocytes, the anonymous exchange of donated oocytes between phenotypically matched donor-recipient pairs,⁴ does not provide such information as in our approach, donated oocytes originate from fertile donors.

The theoretical possibility entertained in the discussion of our paper, that a difference in gonadotropin level might play a role in the higher endometrium receptivity observed in recipients of oocyte donation by comparison with regular IVF patients, is certainly interesting. We wish to stress, however, that it should be considered as very hypothetical. Theoretically, this mechanism could certainly ex-

plain both Check's and our own results: that simple practical applications could easily be implemented to improve endometrium receptivity with exogenous gonadotropins justifies the undertaking of research efforts to determine if this hypothesis sustains experimental verification.

An alternate mechanism that could explain both teams' results would be the presence of an endometrial factor of possible infectious origin, impairing endometrium receptivity and more likely to be present among regular IVF than oocyte donation patients. The high incidence of complete or relative tubal factor in our IVF population (73%) certainly makes this latter hypothesis a plausible one. Our recent observation that in the estradiol (E₂) and progesterone replacement cycle model very high levels of luteal E₂ did not affect endometrial morphology at the presumed time of embryo implantation (cycle day 20)⁵ is further supporting the fact that high E₂ levels probably play little role in lowering implantation rate in IVF cycles.

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"Mad Pursuits"—Markers of Cell Activity?

To the Editor:

We have read with interest the paper by Ren et al.¹ regarding the measurement of placental protein (PP)12 and PP14 in serum for assessing postmenopausal hormone replacement therapy (HRT). Placental protein 14 is a protein synthesized in the glandular cells of the secretory endometrium.² During estrogen-monotherapy, the endometrium will proliferate, and there will be no secretory tissue and consequently no increase in serum PP14. However, during sequential HRT the estrogen-primed endometrium is transformed to secretory phase by the progestogen. The optimal time for assessing the progestational effect in endometrial biopsies is day 6,³ and correspondingly the optimal time for measurement of serum PP14 is at the PP14 peak between day 11 and day 14 after progestogen addition.⁴ It seems that the authors have overlooked the fact that during sequential HRT the postmenopausal endometrium undergoes the same cyclical changes as seen in premenopausal women. The exact time for assessing the specific hormone effect on the postmenopausal endometrium is therefore as essential as it is in premenopausal women.

By selecting optimal times for both blood sampling and endometrial biopsies, we have shown that serum PP14 is highly significantly correlated ($r = 0.70$, $P < 0.001$) with the secretory activity of the endometrium assessed in endometrial samples.⁵ Serum PP14 measured at the optimal time in the tablet cycle thus increased a factor of 5 to 6 of the pretreatment level.

In conclusion the serum concentration of PP14 measured at the optimal time in the tablet cycle accurately reflects the endometrial status and may replace endometrial biopsies during postmenopausal hormone replacement therapy.

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Reply of the Authors:

We appreciate the comments of Drs. Byrjalsen and Thormann who provided us with a preprint of their well-designed study of women receiving sequential estrogen/progesterone replacement therapy from which they concluded that serum placental protein (PP)14 levels accurately reflect the endometrial status and "therefore may replace the invasive endometrial biopsy"¹ They point out that the optimal time for measurement of serum PP14 is between days 11 and 14 after progesterone administration, a finding also reported by Seppala et al.²

In our study, the women were treated on a 28-day cycle basis and received percutaneous estradiol during the first 24 1/2 days and medroxyprogesterone acetate (MPA) for 13 days (not 12 as we originally reported) on days 13 to 25.³ Baseline blood levels of PP14 in the group of patients with secretory endometrium sampled 9 days after the start of MPA rose from 21.6 ± 1.7 (mean \pm SD) to 25.3 ± 2.7 μ /L ($P = 0.01$) and after 12 days of therapy the values rose from 21.5 ± 3.7 to 30.3 ± 4.8 μ g/L ($P < 0.01$). Thus, as we reported, we do find a significant group difference in serum PP14 levels during the last half of the cycle. However, the variable response in individual patients, as well as the small quantitative change in the levels after treatment in this group of patients, prevented us from concluding that PP14 levels are clinically useful as a marker of endometrial status using our treatment protocol.

There are several differences between our study and that reported by Byrjalsen et al.¹ First, their radioimmunoassay for PP14 is 20-fold more sensitive than the assay that we used. Second, their baseline serum PP14 concentrations are 10-fold lower than those found by us or Seppala et al.² Third, different progestogen preparations have different effects on serum PP14 levels, with levonorgestrel

(used in the Byrjalsen study) resulting in a greater rise in serum PP14 concentrations than the MPA used in our study.³ Fourth, our serum PP14 measurements were made in blood samples obtained at the end of 1 year of therapy, whereas Byrjalsen's were made in samples from the first three cycles. They have shown that there is a decreased responsiveness of the endometrium and serum PP14 concentrations after 2 years of estrogen/progestogen administration in comparison with the early months of hormone replacement therapy.¹ Finally, the mean age of the patients in our study was 54.4 years, whereas that in Byrjalsen's study was 51.4 years and, as they suggest,¹ the aging endometrium may be less responsive to progestogens.

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Editorial Comment

Clare Booth Luce is reputed to have said that "the difference between an optimist and a pessimist is that in general the pessimist is better informed." The authors and correspondents reach somewhat different conclusions as to whether placental protein (PP)14 can be used as a marker of secretory activity in the endometrium. The authors are the pessimists, whereas the correspondents are the optimists. This protein, first isolated from human placenta is vintage 1982¹ and is known by several other pseudonyms, including progestogen-dependent endometrial protein and pregnancy-associated endometrial alpha 2 globulin. It belongs to a mosaic of pregnancy associated proteins. More recently it has been shown by im-

munohistochemical techniques to be secreted by the epithelial cells of nonpregnant secretory endometrium.² One has to start with a certain amount of healthy skepticism that a protein measured in blood will reliably predict secretory endometrial activity—better than a serum progesterone or an endometrial biopsy! That is what our Danish correspondents claim, and we will have to see their upcoming publication on this topic.³

The correspondents, in stating that PP14 serum measurements might replace endometrial biopsies, seem to imply that low serum levels of PP14 indicate cellular inactivity. The identification of reliable markers to provide an objective measurement of endometrial cellular proliferation is a "mad pursuit."⁴ The surging interest in the fundamental biology of the cell cycle and cell growth may uncover unique biochemical markers of cell cycle activity, or alternatively of cell growth arrest. In fact, the identification of unique gene products associated with "offenzymes" or with cellular quiescence may be the more productive strategy.⁵ Given the appropriate marker(s), in-situ hybridization or immunohistochemical techniques may allow the assessment of cell activity in clinical specimens and provide information to aid in patient management such as assessing the response to progesterone therapy. Such technology will enable one to study the transcription profile of a tissue like the endometrium in detail. The cell cycle marker of current interest is the protein cyclin, which is a 36KD nuclear protein known as proliferating cell nuclear antigen. The search for such positive and negative markers of cell cycle activity is in high gear with the logical focus being on those proteins that are potentially altered during mitosis.

Paul G. McDonough, M.D., Editor, Letters

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