Dear Sir,

Omland and colleagues’ paper examining the outcome of IVF in a ‘natural cycle’ model to study aetiological differences between endometriosis and other infertility groups interested us (Omland et al., 2001).

Their findings differ from ours and we have tried to understand these differences. It is important to distinguish between this study, which used HCG as a surrogate for the endogenous LH surge when fixed arbitrary criteria were reached, and truly natural cycle programmes, such as ours, devoid of all drugs. Our own programme was designed as a model for studying the mechanisms underlying unexplained and minor endometriosis-associated infertility in completely natural cycles.

We found significantly longer follicular phase, significantly reduced LH surges, significantly lowered LH-Area under the curve (AUC) and reduced fertilization rates in women with minor endometriosis compared with controls, which appear important in final oocyte maturation and inhibiting follicular LH action respectively (Akande et al., 2000; Smith et al., 2002).

Initially, we were at a loss to understand the marked difference in the fertilization rates observed in Omland et al.’s study compared with our own (Cahill et al., 1997) and with the combined data in the literature (Cahill and Hull, 2000). We have some reservations and concerns regarding the results of the statistical analysis as reported. The pregnancy rate per successful oocyte retrieval (P = 0.12) and per embryo transfer (P = 0.14) are not statistically significant using the tests reported and the significantly higher pregnancy rate per initiated cycles reaches significance (P = 0.0497) only when a one-sided P-value is used. The higher fertilization rate in the endometriosis group is non-significant (P = 0.066 using the χ²-test), the proportion of cleaving embryos in each group is very similar (62.2 versus 68%, P = 0.571 using the χ²-test) and the higher cleavage failure with endometriosis is consistent with our observations in completely natural cycles when HCG was not used. Furthermore, endometriosis is associated with defective steroidogenesis in granulosa-lutein cells in both natural and gonadotrophin-stimulated IVF cycles (Harlow et al., 1996). Adding HCG in vitro enhanced progesterone production three-fold and may explain the similar findings in the three groups during the luteal phase.

We agree that unstimulated IVF with HCG supplementation may be an appropriate clinical treatment for minimal endometriosis by overcoming a fundamental defect in women with minor untreated endometriosis, namely reduced LH surge quality. HCG administration may indeed be therapeutically helpful but we disagree that it provides additional information about aetiology. Finally, it seems contradictory to propose adding GnRH antagonists to HCG and still call this ‘natural’ cycle. It could only be ‘unstimulated’ and would likely detract from the lesser expense of ‘natural’ cycle IVF.

Different aetiological mechanisms for unexplained and endometriosis-associated infertility cannot be inferred from unstimulated IVF cycles using HCG to induce ovulation

In addition, the supraphysiological doses of HCG used for ovulation induction might mask these differences.

The truly undisturbed nature of our study allowed for detailed follicular fluid and granulosa cell studies that provided further information on the understanding of endometriosis-associated infertility. Subtle important differences in cortisol and activin levels exist in the preovulatory follicle of infertile women with endometriosis compared with controls, which appear important in final oocyte maturation and inhibiting follicular LH action respectively (Akande et al., 2000; Smith et al., 2002).

References


obtained daily. FSH samples were obtained every other day throughout the cycle as were progesterone from cycle day 9.

The fact that HCG was used after fixed arbitrary criteria, as stated in our paper, would explain the relevant differences between Cahill and colleague’s paper and ours.

We see no conflict in Keay and Cahill’s statement that their determination of follicular phase length, AUC, LH and peak LH measurements more correctly reflect the natural physiological conditions as ours are influenced by the timing of HCG injection and its use. However, our results could reflect a response to HCG in the studied groups that over-ride these differences.

We also appreciate the comments on our statistical results. We regret that some of the data were presented in a way that could confuse the reader as to the choice of method used. We calculated, by means of SPSS, for each patient, the number of fertilized oocytes, the pregnancy rate (PR/initiated cycle, the PR/successful oocyte retrieval and the PR/embryo transfer (Table I). These continuous data were not assumed to be normally distributed. The median, maximum and minimum values for each diagnostic group were left out, causing Keay and Cahill to assume the use of χ², whilst Mann–Whitney was applied. The statistical analyses were approved by the hospital’s Department of Biostatistics. The data given in Table I should clarify these points.

The ascribed cleavage rates by Keay and Cahill of 62.2 and 68% of two of our infertility groups were incorrect. Both the unexplained and the tubal factor groups had a cleavage rate of 100%, whereas the endometriosis-associated group had a cleavage rate of 85% (34/40).

References


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Table I. Data

<table>
<thead>
<tr>
<th></th>
<th>Unexplained infertility</th>
<th>Endometriosis-associated infertility</th>
<th>Tubal infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertilized oocytes (%)</td>
<td>23 (62.2)</td>
<td>40 (80.0)</td>
<td>24 (71.3)</td>
</tr>
<tr>
<td>(median, min-max)</td>
<td>1.00, 0.2</td>
<td>1.50, 1.5</td>
<td>1.00, 1.4</td>
</tr>
<tr>
<td>PR/initiated cycle (n/total)</td>
<td>2.6 (2/77)</td>
<td>10.4 (8/77)</td>
<td>5.8 (4/69),</td>
</tr>
<tr>
<td>(median, min-max)</td>
<td>0.00, 0.00–0.50a</td>
<td>0.00, 0.00–1.00</td>
<td>0.00, 0.00–1.00</td>
</tr>
<tr>
<td>PR/successful oocyte retrieval (n/total, median, min-max)</td>
<td>5.4, (2/37)</td>
<td>16 (8/50)</td>
<td>11.4, (4/35),</td>
</tr>
<tr>
<td>PR/embryo transfer (n/total, median, min-max)</td>
<td>8.7%, (2/23)</td>
<td>23.5%, (8/34)</td>
<td>16.0%, (14/82),</td>
</tr>
<tr>
<td>(median, min-max)</td>
<td>0.00, 0.00–0.50a</td>
<td>0.00, 0.00–1.00</td>
<td>0.00, 0.00–1.00</td>
</tr>
</tbody>
</table>

aP < 0.05 compared with endometriosis-associated infertility (Mann–Whitney).

PR = pregnancy rate.

Dear Sir,

We appreciate the interest of Dr Keay and Dr Cahill in our paper (Omland et al., 2001). Their comment emphasizes the difficulties in comparing results in different study set-ups. We realize, as also pointed out in the paper, that by using HCG for ovulation induction the luteal phase would be influenced, and hormonal values thereafter could only serve as a comparison of this response in the studied infertility groups. We also realized that by using HCG the denomination ‘completely natural cycle IVF’ would be imprecise. We agree that the denomination ‘natural cycle IVF’ perhaps should be reserved for the cases completely free of exogenous medication, but to our knowledge this strict definition is not officially agreed upon. We applied the same method as described by Paulson et al. in 1992 (Paulson et al., 1992) and also used by Daya and referred to by Janssens among others. (Daya et al., 1995; Janssens et al., 2000). The expression ‘Natural cycle IVF’ was used in combination with GnRH antagonist in the publication by Rongières-Bertrand in 1999 (Rongières-Bertrand et al., 1999) and we agree with Dr Keay and Dr Cahill that ‘unstimulated cycle’ in combination with GnRH antagonist would be more precise.

We are of course familiar with the inspiring research by Cahill and colleagues. The logistics of their paper from 1995 (Cahill et al., 1995) with serum samples every 4 hours from follicle diameter >14mm until oocyte recovery, were, alas, an impossibility for our group. Our serum samples were obtained between 0800 h and 0900 h from cycle day 3 to 27. Samples for FSH, LH and estradiol were collected every other day except from cycle day 9 to 17, where estradiol and LH were