Evaluation of serum inhibin A as a surveillance marker after conservative management of tubal pregnancy

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Tubal pregnancy is now commonly managed by laparoscopic salpingostomy or systemic methotrexate. A disadvantage of such conservative management is the need for appropriate follow-up, with serial measurement of serum concentrations of human chorionic gonadotrophin (HCG), to exclude persistent ectopic pregnancy (PEP). Concentrations of inhibin A, also a placental product, are significantly increased during pregnancy and the half-life of inhibin A is significantly shorter than that of HCG. To assess the suitability of inhibin A as a marker of PEP, we studied 16 women who had undergone surgery for a tubal pregnancy, measuring HCG and inhibin during follow-up. The mean ± SEM time taken to achieve non-pregnant concentrations of inhibin A was significantly shorter than for HCG (4.2 ± 0.8 days versus 21.6 ± 4.4 days respectively; P < 0.001 Wilcoxon signed rank test). However, in all women the inhibin A concentration increased rapidly after reaching a nadir, reflecting the return of ovarian function, complicating the interpretation of results. In four women inhibin A was almost undetectable preoperatively, while the corresponding HCG concentration was high. These data suggest that inhibin A will not be a useful marker for PEP but that it may provide a more accurate preoperative assessment of trophoblast viability than HCG, thereby improving management.

Key words: ectopic pregnancy/inhibin/human chorionic gonadotrophin

Introduction

Whereas the traditional surgical management of tubal pregnancy was a salpingectomy performed at open laparotomy, the mainstay of the modern management of ruptured tubal pregnancy has become laparoscopic salpingostomy with laparoscopic salpingectomy preferred when the tube has ruptured (Carson and Buster, 1993; Garry, 1996; Parker and Bisitis, 1997). While some authors have suggested that conservative tubal surgery may confer improvements in subsequent fertility (DeCherney and Kase, 1979; Bruhat et al., 1980), this appears unlikely with future fertility more related to the state of the ipsilateral tube or prior infertility (Hochstein and Baranyai, 1990; Ory et al., 1993). Nonetheless, a laparoscopic approach is associated with important improvements in postoperative recovery and significantly less associated morbidity (Garry, 1996). More recently, the administration of methotrexate to destroy the rapidly dividing trophoblast has gained favour as a treatment in many centres, with results comparable to those achieved with laparoscopic surgery (Seifer et al., 1997).

However, conservative treatment, whether surgical or medical, carries a significant risk (~5%) of inadequately destroying all trophoblastic tissue, leading to persistent ectopic pregnancy (PEP) and a need for further surgical treatment (Seifer et al., 1990; Parker and Thompson, 1994; Dwarakanath et al., 1996). Thus, adequate postoperative surveillance for PEP is an important component of any conservative management. Such surveillance is currently performed with serial assessment of serum human chorionic gonadotrophin (HCG) concentrations. In addition to HCG, the syncytiotrophoblast secretes inhibin A, a heterodimeric glycoprotein hormone composed of an inhibin α and βA subunit characterized by the ability to suppress follicle stimulating hormone secretion from the anterior pituitary (Ying, 1988; Wallace and Healy, 1996). The placental secretion of inhibin A gives rise to maternal serum concentrations which are significantly higher than in the non-pregnancy, with concentrations peaking at 9–10 weeks gestation—an ontogeny similar to HCG (Muttukrishna et al., 1995; Illingworth et al.; 1996, Rombauts et al., 1996). Following pregnancy, inhibin A concentrations, like those of HCG, fall rapidly, reflecting its feto-placental origin (Rombauts et al., 1996; Muttukrishna et al., 1997). Importantly, while the clearance half-life of HCG is ~15 h (Van der Lugt et al., 1985), the clearance half-life of inhibin A is only 45 min (Muttukrishna et al., 1997), offering the possibility that inhibin A may be a useful marker for PEP.

Therefore, we wished to assess whether inhibin A might afford shorter periods of PEP surveillance than HCG, making inhibin A the more suitable marker for the follow-up of women who have undergone conservative tubal surgery for an ectopic pregnancy.

Materials and methods

Between December 1996 and December 1997, 16 women (median age 31 years, range 25–41) with a tubal pregnancy were recruited. Each gave informed written consent and the study had the approval of Monash Medical Centre Human Research and Ethics Committee.

All 16 women had surgical management of their tubal pregnancy. Eleven women underwent laparoscopic salpingostomy and five had...
a salpingectomy. None of the women had PEP requiring further treatment. In all women, blood was collected prior to surgery and twice weekly thereafter until HCG was undetectable, as is routine clinical practice for all women undergoing conservative tubal surgery for ectopic pregnancy in our institution. In each case, serum was separated and stored at −20°C until assay.

HCG was measured using Dade Stratus II total βHCG fluoroenzyme immunoassay (Dade International Inc., Miami, FL, USA). The assay sensitivity was <2 IU/l, with intra- and inter-assay coefficients of variation of 3.8 and 4.4% respectively. Inhibin A was assayed using an enzyme-linked immunosorbent assay (Groome et al., 1994), modified as previously reported (Wallace et al., 1997), but using recombinant human inhibin A (WHO preparation 91/624) as the calibrator. The assay sensitivity was 2 pg/ml with intra- and inter-assay coefficients of variation 5% and 7%, respectively.

Statistical analyses were performed with SPSS for Windows. Hormone data were not normally distributed and were log transformed for correlation analyses. Significance was recognised when $P < 0.05$.

**Results**

Figure 1 shows the mean (SEM) inhibin A and HCG concentrations in the 16 women before and following surgery. Hormonal concentrations declined rapidly, falling by ~62% and 89% in the first 48 h for inhibin A and HCG, respectively. The mean (SEM) time taken to achieve a non-pregnant concentration of inhibin A and HCG was 4.2 (0.8) and 21.6 (4.4) days respectively ($P < 0.001$, Wilcoxon signed rank test). Concentrations of inhibin A increased thereafter in all women (Figure 1).

In seven women, inhibin A became undetectable before HCG, by 7, 7, 7, 8, 29, 43, and 70 days while, in three women, inhibin A and HCG first became undetectable on the same day. In four other women (Table I), while the preoperative HCG concentration was high [mean (SEM) = 481.0 (173.6) IU/l], the corresponding inhibin A concentration was almost undetectable [mean (SEM) = 2.8 (0.16) pg/ml] being within the non-pregnant range and significantly lower than in the other 12 women ($P = 0.004$, Mann–Whitney U test). In the two remaining women, the inhibin A concentration declined only briefly, in the first week, to a concentration consistent with the early follicular phase (9 pg/ml and 12 pg/ml respectively) prior to increasing thereafter, while HCG continued to decline. Maternal serum concentrations of inhibin A and HCG were significantly correlated ($r = 0.82, P < 0.001$).

**Table I. Inhibin A and total βHCG concentrations in the four women with non-pregnant inhibin A concentrations on the day of diagnosis (pretreatment)**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Inhibin A (ng/l)</th>
<th>Total βHCG (UI/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>7.5</td>
<td>479</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>971</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>201</td>
</tr>
<tr>
<td>9</td>
<td>0.8</td>
<td>273</td>
</tr>
</tbody>
</table>

HCG = human chorionic gonadotrophin

**Discussion**

To our knowledge, this is the first study to assess the value of inhibin A as a potential surveillance marker of PEP. Currently, surveillance for PEP has depended upon the monitoring of serum HCG, with a variety of protocols proposed, each differing in sampling frequency and duration (Dwarakanath et al., 1996; Rempen et al., 1996; Hajenius et al., 1997; Parke and Bisitis, 1997). These studies have shown that there is considerable variation between women in the time taken to achieve undetectable HCG concentrations, from only a few days up to five weeks (Dwarakanath et al., 1996; Rempen et al., 1996). In our centre, the average duration of follow-up, for women treated between 1992–97, is 19 days (range 8–53). Further, compared with salpingostomy, the time taken to achieve undetectable HCG concentrations after other conservative approaches, such as methotrexate or expectant management, is significantly longer (Hajenius et al., 1997). Clearly, a shorter follow-up period would be desirable, if possible. In this regard, the half-life of inhibin A, which is also secreted by the trophoblast (Riley et al., 1996; Wallace and Healy, 1996), is 45 min (Muttukrishna et al., 1997), significantly shorter than that of HCG (Van der Lugt et al., 1985; Muttukrishna et al., 1997). However, despite confirming a significantly shorter time taken, on average, to achieve non-pregnant concentrations of inhibin A than HCG, the data presented here suggest that inhibin A will not be a useful marker for PEP.

Maternal serum concentrations of inhibin in women with an ectopic pregnancy are significantly lower than in those with a viable intrauterine pregnancy (Illingworth et al., 1996; Seifer et al., 1996). The pretreatment inhibin A concentrations observed in the 16 women reported here are consistent with this (Figure 1). Therefore, the decline in inhibin A concentration observed in the 16 women after treatment was not as dramatic as reported after early pregnancy termination (Muttukrishna et al., 1997). While this would not be problematic for a marker secreted only by trophoblast, for example HCG, it is for inhibin A which is also secreted by the ovary (Illingworth et al., 1996). Thus, in this study, after an initial decline over the first 3–4 days following surgery, inhibin A concentrations progressively increased – a pattern that would be consistent
with either PEP or the return of normal ovarian function. Given the low circulating concentrations of inhibin associated with tubal pregnancy, without the HCG data it would not have been possible to discern easily which of these possibilities applied in any given woman. None of the women reported here had PEP, and it is still possible that the postoperative serum inhibin A profile in such cases is different. Nonetheless, as discussed, it would be expected that absolute inhibin A concentrations would be modest compared with those of normal pregnancy, and it would remain difficult to differentiate PEP from ovarian activity using inhibin A alone. Given the clarity afforded by HCG in this setting, we would suggest that inhibin A is unlikely to be useful as a surveillance marker.

Interestingly, in four women with preoperative serum HCG concentrations sufficiently high to require surgery, inhibin A was almost undetectable and significantly lower than in the other 12 women. It is possible that the ectopic trophoblast in these women was non-proliferative prior to surgery, as indicated by the low inhibin A, and that intervention in these women was unnecessary. This would not be evident with HCG, however, simply because of its longer half-life. Therefore, in those centres that do not favour an expectant management of ectopic pregnancy, inhibin A might be useful to assess the need for surgery or methotrexate. While this potential use requires further prospective evaluation, if it is confirmed, then 25% (4/16) of the women in this study would have avoided surgery.

In summary, while our data show that the clearance of inhibin A after removal of an ectopic pregnancy is more rapid than that of HCG, the early resumption of ovarian function complicates the interpretation of inhibin A concentrations and argues strongly against inhibin A as a valuable surveillance marker for PEP. In contrast, pretreatment inhibin A may provide a more accurate assessment of the viability of ectopic trophoblastic tissue than HCG, thereby guiding management better. Further evaluation of this possibility would be worthwhile.

Acknowledgements

This study was supported by the Faculty of Medicine, Monash University.

References


Received on January 16, 1998; accepted on May 21, 1998