Bilateral oophorectomy in a pregnant woman: hormonal profile from late gestation to post-partum: Case report

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BACKGROUND: A 16 week pregnant woman presented with massive theca–lutein cysts requiring bilateral oophorectomy. Pregnancy progressed uneventfully and spontaneous lactation ensued after delivery. METHODS: To study the role of the ovary on the hormonal profile at the end of gestation and in post-partum, we measured FSH, estradiol (E2), unconjugated estrone (E1), unconjugated estriol (E3), sex hormone-binding globulin, progesterone, dehydroepiandrosterone sulphate and prolactin at 37 weeks gestation and at 8 h, 4 days, 5 weeks, and 2 months post-partum. RESULTS: These hormones were within the range expected for ovary-intact pregnant and puerperal women until 4 days post-partum. At 5 weeks post-partum, FSH increased to a peri-menopausal range (31.4 IU/l) while estrogens remained within the normal puerperal range (E2 = 239 pmol/l; E1 = 102 pmol/l), contrasting with their rapid changes in non-pregnant women after bilateral oophorectomy. At 2 months, while partially breastfeeding, FSH, E2 and E1 were closer to menopausal range (68 IU/l, 136 and 70.2 pmol/l respectively), and hormone replacement was started. CONCLUSIONS: We conclude that the ovary is not required to maintain a normal hormonal profile in late pregnancy and early puerperium. However, the increase in FSH to peri-menopausal levels at 5 weeks post-partum, despite breastfeeding, suggests that the ovary is needed to maintain low FSH concentrations during lactation.

Key words: bilateral ovariectomy/estrogens/FSH/pregnancy/premature menopause

Introduction

It is well established that the ovary is not required to maintain pregnancy after the first trimester in the human species. Removal of the corpus luteum at 10 weeks gestation does not cause a decrease in progesterone or its metabolites and does not compromise the maintenance of pregnancy (Csapo et al., 1973). These findings are confirmed by reports of women undergoing bilateral oophorectomy after the first trimester of pregnancy with subsequent normal evolution of pregnancy and term deliveries (McCormack et al., 1983; Colavita et al., 1996). A similar situation occurs in the animal species in which the placenta is the main source of progesterone after initial gestation, as in the equine species. Ovariectomized mares used as recipients for embryo transfer require progesterone supplementation only during the first third of gestation, oophorectomy not representing an endocrine risk for the continuation of gestation until term or for milk production after parturition (Hinrichs et al., 1987). In women, the hormonal profile during physiological pregnancy is well known, characterized by a marked increase in plasma concentrations of estrogens and progesterone (Tulchinsky and Hobel, 1973; O’Leary et al., 1991; Laird and Parsons, 1996). Prolactin (PRL) rises continuously from early pregnancy in correspondence with augmenting estrogen levels, and the breast undergoes secretory transformation in preparation for lactation by influence of PRL acting in concert with estrogens and progesterone (Evans et al., 1990). The withdrawal of progesterone after delivery, together with the sharp rise in circulating PRL induced by suckling, initiate and maintain milk production (Salzman and Cooke, 1996).

Other studies have measured changes in hormones in late pregnancy and in lactational amenorrhea in ovary-intact women (Díaz et al., 1991; Tay et al., 1992; Perheentupa et al., 2000; Campino et al., 2001). These reports describe plasma concentrations of FSH and E2 comparable to those in the follicular phase of the normal menstrual cycle, indicating an inhibition of FSH during lactation.

The role of the ovary in the gonadotrophin suppression during lactation has been studied in different mammalian species: human, non-human primates, sheep, cow, pig, and rat (reviewed in McNeily, 1994). In these species suckling plays a major role in the suppression of gonadotrophin output.
from the pituitary during lactation (Gordon et al., 1992; Ördög et al., 1998; reviewed in McNeilly, 1994). Ovariectomy of nursing rhesus monkeys, in contrast to the rapid increase in LH after ovariectomy in cycling females (Atkinson et al., 1970), resulted in a prolonged delay in the elevation of gonadotrophins (Weiss et al., 1976); these findings suggested an ovary-independent mechanism whereby suckling suppresses gonadotrophins.

There are no studies evaluating the hormonal profile in ovariectomized pregnant and nursing women. In the case we report, emergency bilateral oophorectomy at week 16 of gestation, due to complications of massive theca–lutein cysts, did not interfere with the continuation of pregnancy to term nor with lactation as could be predicted by the knowledge of the endocrine physiology of pregnancy. This unique model stimulated us to study the ovary’s role in the hormonal profile at the end of gestation and in lactation and, in particular, to investigate for the first time, the post-partum changes of FSH whilst breastfeeding in the absence of ovaries.

Case report
A 31 year old woman, gravida 3, para 2, with normal menstrual history and uneventful previous pregnancies and deliveries, was seen initially at 8 weeks gestation with a single intrauterine pregnancy. A pelvic ultrasound showed multicystic ovaries, $5 \times 3.5 \text{ cm}$ each. Two weeks later she was admitted to the hospital because of abdominal pain. Pelvic ultrasound revealed bilateral ovarian tumours with multiple loculations (right ovary $= 13.2 \times 8.0 \text{ cm}$; left ovary $= 13.4 \times 9.7 \text{ cm}$) with no ultrasound evidence of molar pregnancy. The patient was admitted for observation, discharged home when the pain settled, and advised to rest. At 16 weeks gestation she was admitted again due to acute abdominal pain, nausea, and vomiting. Physical examination revealed a very large abdominal mass, extending from the pelvis to the ribs, no signs of hyperandrogenism, positive Blumberg sign, heart rate of 100 beats/min, blood pressure 130/90, and temperature 37.2°C. Abdominal ultrasound showed giant loculated ovarian tumours, $\sim 19 \times 15 \text{ cm}$ each, and a normal fetus and placenta. Emergency exploratory laparotomy revealed ascites, a giant right ovarian tumour (1064 g), and a partially ruptured giant left ovarian tumour (891 g). Bilateral oophorectomy was performed. Subsequent histopathology diagnosed giant bilateral lutein cysts. The patient’s post-operative course was unremarkable, and she progressed uneventfully to term. She delivered spontaneously a 3880 g and 52 cm male infant at 39 weeks. The placenta weighed 600 g and was of normal macroscopic appearance.

Lactation commenced spontaneously, and she fully breastfed for 10 days, after which she maintained partial breastfeeding until 10 weeks post-partum, a pattern similar to her previous pregnancies. HRT (transdermal E$_2$ 50 µg/day plus oral medroxyprogesterone acetate 5 mg for 12 days per cycle) was commenced at 2 months post-partum because E$_2$ concentration decreased to 136 pmol/l, although the patient experienced no climacteric symptoms. Two weeks later she discontinued lactation.

The patient’s body mass index at the beginning of pregnancy was 26.2 kg/m$^2$ and 1 month post-partum was 27.8 kg/m$^2$.

Study protocol
We measured serum FSH, E$_2$, unconjugated estrone (E$_1$), unconjugated estriol (E$_3$), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S) and PRL at 37 weeks gestation and at 4 days, 5 weeks, and 2 months post-partum. Post-suckling PRL was also measured at 4 days, 5 weeks, and 2 months post-partum. Progesterone was measured at 37 weeks gestation and at 4 days and 5 weeks post-partum. Finally, at 3 months post-partum, after weaning and under HRT, we measured FSH, E$_2$, SHBG, and PRL. We did not measure LH at any time.

Laboratory assays
The study of this patient was contemporary with the study by Campino et al. (2001). The same assays were used in both studies to measure E$_2$, E$_1$, SHBG, progesterone, DHEA-S, and PRL. The inter-assay coefficients of variation were: 10.8% for the 1619 pmol/l plasma pool for E$_2$; 9.1% for the 1184 pmol/l E$_1$ plasma pool; 11.2% for the 9.1 nmol/l E$_3$ plasma pool; 7.0% for the 68.5 nmol/l plasma pool for SHBG; 7.8% for the 3.93 nmol/l plasma pool of pregnancy sample progesterone; 8.0% for the 5780 nmol/l plasma pool for DHEA-S; and 9.5% for the 27.7 µg/l plasma pool for PRL. The intra-assay coefficients of variation (CV) were <10% for all the measurements.

FSH concentration was measured by the automated chemiluminescence system (ACS: Centaur; Bayer, USA), using as a standard the Second International Reference Preparation of hMG from the National Institutes of Health (2nd IRP-hMG). This standard was calibrated against LER 907 (human pituitary gonadotrophin extract prepared by Dr Leo E.Reichert Jr); 53 IU of FSH 2nd IRP-hMG correspond to 1 mg of LER 907 (Rosemberg, 1979). Inter-assay CV was 9.6% for the 4.35 IU/l plasma pool and 8.7% for the 13.6 IU/l plasma pool. Intra-assay CV was 3% for concentrations of 6–144 IU/l.

Results
The sequential changes in E$_2$, SHBG and FSH plasma concentrations from the end of gestation, through puerperium, and up to 3 months post-partum in this oophorectomized nursing woman are presented in Figure 1. E$_2$ showed a prompt decrease after delivery, to reach 136 pmol/l at 2 months post-partum. FSH concentration was low at 37 weeks gestation and remained low in the samples taken 8 h and 4 days after delivery, but increased considerably at 5 weeks post-partum (31.4 IU/l) to reach 68 IU/l at 2 months post-partum, while the patient was partially breastfeeding. One month of HRT resulted in a small increase in E$_2$ plasma concentration (294 vs 239 pmol/l at 5 weeks post-partum) but had a strong impact on plasma FSH, which decreased to 17.8 IU/l. Plasma SHBG concentration was elevated at 37 weeks gestation (>500 nmol/l) and remained high in the early puerperium,
decreasing by 5 weeks post-partum to remain at low levels thereafter (<100 nmol/l).

The comparison of hormone concentrations in this oophorectomized patient with those of ovary-intact women at 38 weeks of pregnancy (Table I) shows a higher progesterone concentration (1256 nmol/l) at 37 weeks gestation in the patient, whereas the concentrations of all estrogens, SHBG, DHEA-S and PRL were within the range of values in ovary-intact pregnant women (Campino et al., 2001). In early puerperium (8 h and 4 days post-partum), the hormonal profile of this oophorectomized patient did not show major differences from the values described at this stage of puerperium in ovary-intact breastfeeding women by Shaaban et al. (1987). However, comparing hormone concentrations in this patient with those of ovary-intact women at 1 and 2 months post-partum (Table II), a 4 to 5-fold difference in FSH concentration between the oophorectomized patient and ovary-intact breastfeeding women (Díaz et al., 1991) became apparent at 5 weeks post-partum, whereas the other hormones remained within the range described for ovary-intact breastfeeding women (Campino et al., 2001). The difference in FSH concentration between our patient and ovary-intact breastfeeding women increased further, reaching ~8.5-fold at 2 months post-partum. The concentrations of E2 and E1 in the patient decreased by 43 and 31% respectively during this interval, but E2 levels still were within the range reported in ovary-intact breastfeeding women (Campino et al., 2001). The difference in FSH concentration between our patient and ovary-intact breastfeeding women increased further, reaching 8.5-fold at 2 months post-partum. The concentrations of E2 and E1 in the patient decreased by 43 and 31% respectively during this interval, but E2 levels still were within the range reported in ovary-intact breastfeeding women (Table II) (Díaz et al., 1991).

The high plasma concentrations of SHBG in pregnancy showed a normal descending curve through puerperium. DHEA-S increased within 4 days of delivery, showing a normal ascending pattern up to 2 months post-partum. Basal and post-suckling PRL concentrations were similar to those of normal breastfeeding women at 5 weeks post-partum (Campino et al., 2001) (Table II).

After 1 month under HRT and 2 weeks after weaning, plasma E2 concentration increased slightly, and FSH decreased to values similar to those described in estrogen-treated menopausal women (Barnes and Levrant, 1999; Speroff et al., 1999). Basal PRL concentration (10.2 μg/l) and SHBG (49 nmol/l) reached the levels described in non-nursing women (Campino et al., 1999).

Figure 1. Changes in estradiol, sex hormone-binding globulin and FSH concentrations from 14 days prior to delivery (37 weeks of gestation) until 90 days after delivery in an oophorectomized nursing woman. E2 = estradiol; SHBG = sex hormone-binding globulin.

### Table I. Hormonal profile at 37 weeks of gestation in an oophorectomized woman compared to non-oophorectomized pregnant women at 38 weeks

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Patient</td>
<td>6.1</td>
<td>78.2</td>
<td>15.1</td>
<td>60.8</td>
<td>539</td>
<td>1256</td>
<td>814</td>
<td>251</td>
</tr>
</tbody>
</table>

Values from the controls are expressed as a range and correspond to a study in normal Chilean pregnant women (n = 8) who maintained amenorrhoea for >6 months post-partum (Campino et al., 2001).

E2 = estradiol; E1 = unconjugated estrone; E3 = unconjugated estriol; SHBG = sex hormone-binding globulin; DHEA-S = dehydroepiandrosterone sulphate; NM = not measured.

### Table II. Post-partum hormonal profile in an oophorectomized nursing woman

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</thead>
<tbody>
<tr>
<td>8 h</td>
<td>&lt;4.0</td>
<td>4864</td>
<td>4248</td>
<td>1875</td>
<td>517</td>
<td>NM</td>
<td>NM</td>
<td>235 basal</td>
</tr>
<tr>
<td>4 days</td>
<td>5.9</td>
<td>202.2</td>
<td>333</td>
<td>608</td>
<td>466</td>
<td>4.3</td>
<td>1358</td>
<td>212/245</td>
</tr>
<tr>
<td>5 weeks</td>
<td>31.4</td>
<td>239</td>
<td>102</td>
<td>486</td>
<td>56</td>
<td>&lt;1.6</td>
<td>3260</td>
<td>145/179</td>
</tr>
<tr>
<td>Controls</td>
<td>0.9–6.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73–426&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77–307&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NM</td>
<td>55–181</td>
<td>0.4–3.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NM</td>
<td>21–155/98–357</td>
</tr>
<tr>
<td>2 months</td>
<td>68.0</td>
<td>136</td>
<td>70.2</td>
<td>&lt;347</td>
<td>47</td>
<td>NM</td>
<td>NM</td>
<td>4620</td>
</tr>
<tr>
<td>Patient</td>
<td>1.2–8.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51–360&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NM</td>
<td>NM</td>
<td>0.4–2.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NM</td>
<td>NM</td>
<td>111/135</td>
</tr>
<tr>
<td>Controls</td>
<td>399</td>
<td>136</td>
<td>70.2</td>
<td>&lt;347</td>
<td>47</td>
<td>NM</td>
<td>NM</td>
<td>4620</td>
</tr>
</tbody>
</table>

Values from the controls (n = 10), expressed as a range, correspond to the study by Campino et al. (2001), except those marked with<sup>a</sup>, which correspond to the study (n = 25) by Díaz et al. (1991). Control values correspond to normal Chilean fully nursing women who maintained amenorrhoea for >6 months post-partum. Samples were not collected at 8 h and 4 days post-partum in the controls. For abbreviations, see Table I.
Discussion

We present the case of a woman requiring bilateral oophorectomy during the second trimester of pregnancy due to the complications of massive theca–lutein cysts. In this patient, the normal evolution of pregnancy and the spontaneous establishment of breastfeeding confirmed that the ovary is not necessary after the first trimester of pregnancy to maintain pregnancy and to initiate lactation, as has been previously reported (McCormack et al., 1983; Colavita et al., 1996).

The plasma concentrations of estrogens at the end of gestation in this patient were similar to those in normal pregnant women (Campino et al., 2001). This was expected since, in normal pregnancy, E₂ and E₁ are synthesized by placental aromatization of maternal and fetal adrenal androgens, mainly DHEA-S (Siiteri and MacDonald, 1966). Enhanced utilization of DHEA-S in pregnancy lowers maternal plasma DHEA-S levels (Gandy, 1977; O'Leary et al., 1991). This was confirmed in this patient by the low concentration of DHEA-S at 37 weeks of gestation that increased to normal non-pregnant levels through puerperium (Gandy, 1977).

Progesterone concentration at 37 weeks gestation was above the range described in ovary-intact normal pregnant women (Campino et al., 2001). Estrogens increase low density lipoprotein cholesterol uptake by the human placenta (Grimes et al., 1996) and also increase cytochrome P450 side-chain cleavage enzyme activity in baboon placental microsomes regulating the conversion of cholesterol to pregnenolone, the precursor of progesterone (Babischkin et al., 1997). We do not know whether the increased plasma progesterone concentration was due to more efficient utilization of substrate or to increased placential enzymatic activity.

Normal estrogen concentrations during pregnancy explain the normal values of SHBG and PRL observed in this patient during pregnancy and postpartum, since estrogens induce the hepatic synthesis of SHBG (Odlin et al., 1982) and stimulate PRL production in the pituitary (Yamamoto et al., 1986; Blum et al., 1987; Porter et al., 1990; Scheithauer et al., 1990). The low plasma concentration of FSH observed at the end of gestation in the patient may be explained by the suppressive effects of pregnancy hormones upon the hypothalamic–pituitary axis (McNeilly, 2001).

In contrast to the lack of involvement of the ovary in determining the normalcy of reproductive hormones during pregnancy as just discussed, our data suggest that suckling may require the ovary to fully exert its gonadotrophin-suppressing effect. In this oophorectomized nursing patient, basal and post-suckling PRL responses were normal at 5 weeks post-partum, and FSH was normally suppressed in the early puerperium (8 h and 4 days after delivery). The latter could be due to an after-effect of high sex steroids during pregnancy, as shown in nursing and non-nursing ovary-intact women in whom basal FSH concentration is low and its response to GnRH is suppressed until the third week post-partum (Canales et al., 1974; Keye and Jaffe, 1976). Therefore, the evolution of post-partum FSH levels in our patient differed from those in ovary-intact breastfeeding women. FSH increased to a peri-menopausal range by 5 weeks after delivery, reaching a close-to-menopausal range at 2 months post-partum, suggesting that the suppressive effect of suckling upon gonadotrophins was reduced in the absence of the ovaries. However, the change of FSH in our patient contrasts with the rapid increase in gonadotrophins (4 days) in non-pregnant women after bilateral oophorectomy (Yen and Tsai, 1971; Alexandris et al., 1997), suggesting that suckling restrained the expected gonadotrophin rise in the absence of ovaries. This inhibitory effect of lactation has been described experimentally in ovariectomized nursing rhesus monkeys (Weiss et al., 1976). In the patient, suckling episodes may have been insufficient to suppress FSH as she did not fully breastfeed; thus, the possibility that the gonadotrophin-suppressing effect of suckling required the presence of the ovary remains open.

In this patient, E₂ remained in normal puerperal range and slightly higher than in non-pregnant oophorectomized women (Alexandris et al., 1997). As she was overweight, it is likely that estrogens were derived from peripheral conversion from adrenal androgens in fat tissue (Hansen et al., 1997; Arlt et al., 1998; Dragojevic et al., 2004). At 2 months post-partum, when FSH was close to the menopausal range, the patient was started on 50 μg/day transdermal E₂ replacement therapy, a dose which has been demonstrated not to interfere with lactation (Perheentupa et al., 2000), and FSH decreased as occurs in post-menopausal women treated with HRT. Consistent with her previous nursing history, lactation ended 70 days after delivery.

To summarize, the present data suggest that the gonadotrophin-suppressing effects of suckling during lactation may require involvement of the ovary in women. Pregnant and breastfeeding women who have suffered premature ovarian failure and achieved pregnancy following oocyte donation and IVF may offer further opportunities to explore this possibility.

Acknowledgements

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