SEX HORMONE CHANGES UNDERLYING MENSTRUAL DISTURBANCES ON HAEMODIALYSIS


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Summary

Sequential changes in luteinising hormone (LH), follicle stimulating hormone (FSH), oestradiol (E₂), progesterone (PROG), prolactin (PRL) and testosterone (T) were studied throughout the menstrual cycle in ten women on regular haemodialysis. At the time of study seven women were menstruating and three had secondary amenorrhoea. Only one patient had regular menses.

In none of the 15 cycles studied was there a normal luteal phase with an adequate PROG rise, although 9 cycles (4 patients) had E₂ changes suggesting that ovulation may have occurred. Increased PRL and T levels were found in 9 and 6 women respectively.

These hormonal abnormalities can be related to the menstrual disturbances and explain the low fertility seen in these patients. Bromocriptine or prednisolone may prove useful in their treatment.

Introduction

Menorrhagia [1], menstrual irregularity, secondary amenorrhoea [2] and reduced fertility [3] are common problems in women on regular dialysis therapy (RDT). Although altered luteinising hormone (LH), follicle stimulating hormone (FSH), oestradiol (E₂) and prolactin (PRL) are reported in these patients [4,5] there is little information on either the sequential changes in sex hormones throughout menstruation and hence the incidence of ovulation or the interrelationship between menstrual disturbance, reduced fertility and abnormal hormone levels. We have therefore investigated serial changes in LH, FSH, E₂, progesterone (PROG), PRL and testosterone (T) in females on RDT and the changes seen in two women following treatment with bromocriptine, a long acting dopamine agonist that lowers PRL levels [6], and successful transplantation.
Patients

Ten women aged 14.3–46.8 years and established on home RDT for 0.5–6.7 years consented to the study. All dialysed three nights a week for 8–10 hour sessions. Two used an Organon-Technika REDY system with Gambro Lundia dialysers (1 m²); the rest had a Dylade series B proportionating system and Meltec Multipoint dialysers (1 m²). None were taking any prolactin raising drug, oestrogen, progesterone or had had cytotoxic therapy. Each was studied for three menstrual cycles or, if menses were irregular, a minimum of twelve weeks.

Patient Assessment

A careful gynaecological history was obtained and a full clinical examination carried out, noting in particular galactorrhoea, hirsutes or any gynaecological abnormality. Daily basal body temperature charts were kept by the patients and, once a week, blood was taken just before dialysis. These samples were all obtained at 20.00–23.00 hours, 36–40 hours after the last dialysis, for measurement of plasma \( E_2 \) and PROG and serum LH, FSH and PRL. In addition, because of diurnal variation of T, samples for this and sex hormone binding globulin (SHBG) were collected monthly between 0900–1000 (26 hours post dialysis). All samples were stored at \(-20\)°C and then analysed together to avoid interassay variation. Using the Vickers M300 analyser, albumin [7], creatinine [8], and urea [9], were also measured monthly, 26 hours post dialysis.

Assays

LH, FSH and PRL were measured by specific double antibody radioimmunoassays using MRC standards 68/40 for LH and 69/104 for FSH [10] and 71/222 for PRL [11]. T was measured by radioimmunoassay, after extraction with SHBG as described [12]. PROG was measured by radioimmunoassay after extraction in petroleum ether using an antibody that had significant cross reaction with nothing except 11 \( \alpha \) OH progesterone (54%), corticosterone (2%) and 17 \( \alpha \) OH progesterone (0.12%). \( E_2 \) was measured by specific radioimmunoassay using an antiserum raised in goats and conjugated at C6 to bovine serum albumin.

Results

Gynaecological History

Before the onset of chronic renal failure (CRF), eight patients had had regular 28 day cycles and six had been pregnant (12 pregnancies and 3 miscarriages). The remaining two patients (aged 16.7 and 14.3 yr) had had their menarche when already in CRF at 14.4 and 12.7 yr respectively. At the time of study only one had regular cycles (27 days); six women were menstruating
irregularly (cycle length 29–100+ days) and three women had secondary amenorrhoea (0.5–3.5 yr). One incomplete and fourteen complete cycles were studied.

**Clinical Examination**

One patient had bilateral galactorrhoea. No other relevant abnormalities were detected.

**Basal Body Temperature Charts**

All patients, except two with secondary amenorrhoea, completed these. None showed a mid cycle fall or a luteal temperature rise.

**Hormonal Changes**

*Oestradiol (normal follicular value 74–257 pmol/litre and Progesterone (normal luteal rise to > 40 nmol/litre)*

Mean follicular E₂ levels were normal (mean ± 1 SD, 258 ± 142 pmol/litre) except in one woman with secondary amenorrhoea who had low values (40 ± 19 pmol/litre) and one woman with raised values (500 ± 62 pmol/litre). Luteal E₂ increased in four of the seven menstruating patients. Two showed mid cycle E₂ peaks characteristic of ovulation as illustrated in Figure 1, which shows hormonal changes in the one patient who was menstruating regularly. These four patients also had a rise in luteal PROG but this was subnormal in all and the highest luteal levels in each patient ranged from 7.5–27.2 nmol/litre. In the remaining six patients, there were no significant E₂ or PROG rises.

**Gonadotrophins**

*(Normal follicular LH 2.5–21 U/litre and FSH 1–10 U/litre)*

Two women (aged 46 and 45 yr) had markedly elevated LH and FSH levels, in one (LH > 64 U/litre, FSH > 50 U/litre) this was associated with amenorrhoea, and in one (LH 27.1 U/litre, FSH 21 U/litre) with irregular menses. The remaining eight had normal FSH levels (mean 5.0 ± 2.6 U/litre). LH was slightly elevated in three patients (mean 22.2 ± 1.2 U/litre) but normal in the rest (mean 11.3 ± 6.3 U/litre).

**Prolactin**

*(Normal < 360 mU/litre)*

PRL was raised in all patients but the range of variation was wide (377–2405 mU/litre).
Testosterone and Sex Hormone Binding Globulin
(Normal $T < 2.7$ nmol/litre and SHBG $4.2-11.3 \times 10^{-8}$ M)

Mean serum $T$ was increased in six menstruating patients, ranging from 3.2–5.2 nmol/litre but was normal in the three women with secondary amenorrhoea (1.5–2.6 nmol/litre). Mean SHBG was normal ($6.4 \pm 2.8 \times 10^{-8}$ M).

Biochemistry

Mean values were: albumin $42.4 \pm 2.4$ G/litre, creatinine $708 \pm 188$ $\mu$mol/litre and urea $16.4 \pm 6.0$ mmol/litre. There was no correlation between these values and the hormone levels observed.
Effects of Treatment

1. By Renal Transplantation

One patient received a cadaver renal graft four months after she was originally studied. Her menses were then irregular (Figure 2) but within two months of transplantation she developed a regular 28 day cycle with improvement in symptoms of dysmenorrhoea and menorrhagia. Six months post transplant, one cycle was studied when plasma creatinine was 60 μmol/litre and she was taking prednisone 20 mg/day and azathioprine 100 mg/day. Results are shown in Figure 2. A mid cycle rise in LH and E₂ was seen and luteal PROG rose to 17.4 nmol/litre. Serum T fell from 5.2 to <1 nmol/litre but SHBG levels did not alter.

Figure 2. Changes in PRL, FSH, LH, E₂ and PROG in a patient aged 16 yr throughout two menstrual cycles (1) on RDT and (2) six months following transplantation
Figure 3. Changes in PRL, FSH, LH, E₂ and PROG in a patient aged 25 yr with secondary amenorrhoea on RDT (1) before treatment and (2) during a menstrual cycle on bromocriptine therapy.
2. With Bromocriptine

One woman, when studied, had had secondary amenorrhoea for 3.5 years and galactorrhoea associated with marked hyperprolactinaemia (Figure 3); she was treated with bromocriptine 2.5 mg tds. Galactorrhoea disappeared and after four months on treatment she started to menstruate. Results of studying the first cycle are also shown in Figure 3. PRL fell from 2405 ± 421 mU/litre to 75 ± 19 mU/litre. A luteal increase in E₂ and PROG were seen.

Discussion

We have confirmed that menstrual problems are common in women on RDT. The lack of a normal luteal rise in PROG in any of the cycles studied means abnormal function of the corpus luteum and explains the infertility seen in these patients.

Hormone abnormalities in the seven women who were menstruating differed from those with secondary amenorrhoea. In the former group all seven had mild hyperprolactinaemia (< 1,000 mU/litre). One (aged 45 yr) formed a separate case as she had markedly raised gonadotrophin levels indicating that she was peri-menopausal. The remaining six however all had a raised serum T with an elevated LH in two cases.

Hyperprolactinaemia is associated with infertility and menstrual disturbance, usually amenorrhoea [13], and raised PRL levels are known to affect the production of PROG by the corpus luteum [14]. The poor luteal PROG rises could therefore be secondary to hyperprolactinaemia.

Raised serum T is typical of the polycystic ovary syndrome (PCO) and a proportion of these patients also have elevated follicular LH levels and hyperprolactinaemia [15]. Solitary ovarian cysts occur more frequently in women on RDT [16] but we are unaware of any reports of polycystic ovarian changes. PCO is an extremely common cause of menstrual disturbance and infertility and suppression of abnormal androgen production using steroids may restore gonadal function to normal [15]. It is therefore possible that in the patient who was transplanted, the onset of regular menstruation and the fall in serum T were associated either with the return of normal renal function or the use of steroids for immunosuppression. This improvement occurred despite persistent mild hyperprolactinaemia which itself could account for the inadequate luteal rise seen after transplantation.

In the three women with secondary amenorrhoea separate abnormalities were identified. In one patient markedly raised PRL levels were associated with galactorrhoea, and treatment with bromocriptine, as recommended for the amenorrhoea-galactorrhoea syndrome [6], restored PRL to normal and menstruation recommenced. Further studies are necessary to confirm whether she is now ovulating. The second patient in this group had markedly elevated gonadotrophin levels typical of the menopause while the third woman had recently lost weight from 52 kg to less than 45 kg, and her amenorrhoea was thought to be secondary to this.
Menstrual disturbance and infertility on dialysis can therefore be related to the sex hormone abnormalities seen. We have not identified a single pathology specific to CRF but several endocrine abnormalities which can be associated with menstrual problems. Therapeutic measures such as treatment with bromocriptine or prednisolone could therefore become a useful form of treatment for these endocrine abnormalities.

Acknowledgments

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References

4 Øgaard, K, Hagen, C and McNeilly, AS (1975) Acta Endocr., 80, 237
12 Green, JRB, Goble, HL, Edwards, CRW and Dawson, AM (1977) Lancet, i, 280

Open Discussion

BRUNNER (Basel) Excessive menstrual bleeding is very often a great problem in girls or in young women on dialysis. In your patient whom you treated with bromocriptine did you get excessive bleeding or acceptable amounts of bleeding?

WASS Do you mean when she was on bromocriptine?

BRUNNER During the treatment with bromocriptine.

WASS Her menstruation has been within normal limits on bromocriptine, but slightly heavy on her dialysis nights. Regarding the girl who had the transplant; beforehand she had markedly heavy bleeding, but this all settled down following transplantation.

BRUNNER So would you say that with bromocriptine you might reduce exces-
sive bleeding to normal bleeding?

WASS Well the bromocriptine was used in the patient who had amenorrhoea. But certainly menorrhagia can be a feature of both high prolactin levels or a feature of the polycystic ovary syndrome.

BRUNNER Did the patient prefer to have this bleeding or did she prefer not to have bleeding at all?

WASS The patient who was treated very much wanted to have her periods back. She should like to have another baby in fact.