OESTROGEN TREATMENT AND SUBSEQUENT PREGNANCY IN TWO PATIENTS WITH SEVERE HYPERGONADOTROPHIC OVARIAN FAILURE

By

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ABSTRACT

This report describes in detail the histological and hormonal findings in a patient with Turner's syndrome (45,XO) and a patient with premature menopause (46,XX), who both conceived after withdrawal or reduction of substitution therapy with oestrogens. The aetiology of severe hypergonadotrophic ovarian failure is discussed, and theories regarding a possible relationship between the oestrogen treatment and subsequent pregnancy are hypothesized.

Severe hypergonadotrophic ovarian failure is characteristic of the following diseases: 1) gonadal dysgenesis with 45,XO chromosome complement (Turner's syndrome), 2) gonadal dysgenesis with 46,XX chromosome complement, 3) premature menopause and 4) the resistant ovary syndrome.

The manifestations of gonadal dysgenesis may vary considerably, ranging from the classical Turner's syndrome (Turner 1938) to the patient, who has the solitary anatomic abnormality of a rudimentary streak gonad. Such patients may have some ovarian function, at least for a limited period of time (Groll & Cooper 1976; Mc Donough & Tho 1974), and even pregnancies have been achieved in a very few cases (Bahner et al. 1960; Grace et al. 1973; Nakashima & Robinson 1971; Philip & Sele 1976).
In addition to the increased gonadotrophin levels, the criteria for the diagnosis of premature menopause and the resistant ovary syndrome are secondary amenorrhoea before the age of 30 years and normal or slightly underdeveloped secondary sexual characteristics. The difference is that patients with the resistant ovary syndrome have a morphological normal, but non-responsive ovarian follicular apparatus in contrast to patients with premature menopause, who have only very few primordial and atretic ovarian follicles left (Emperaire et al. 1970; Seegar Jones & Moraes-Ruehsem 1969; Starup & Sele 1973; Starup et al. 1971; Zárate et al. 1970). Also in these patients a few pregnancies have been reported (Polansky & de Papp 1976; Reyes et al. 1976; Shapiro & Rubin 1977).

Because of its rarity it was found of interest to give a detailed report of the histological and hormonal findings in a patient with Turner’s syndrome and a patient with premature menopause, who both conceived after withdrawal or reduction of oestrogen treatment and went through successful pregnancies. Chromosome studies in the first mentioned patient have been published previously (Philip & Sele 1976).

CASE REPORTS AND RESULTS

Case 1

K. H. 33 years. Referred to our department when 15 years old because of dwarfism. Height: 133 cm, weight: 38 kg. She had no secondary sexual characteristics, a slight cubitus valgus but no pterygium colli or other malformations. Her parents and an older sister were all of normal height. Chromosome analysis of peripheral blood and skin showed a 45.XO complement without any evidence of mosaicism, and this finding was later confirmed in the uterus and both ovaries. She had a high excretion of total gonadotrophins (> 60 MU/24 h) and a low excretion of total oestrogens (< 20 MU/24 h). The thyroid and adrenal function were normal.

Substitution therapy with dienestrol acetate 5 mg daily for 3 weeks combined with norethisterone 5 mg daily for 1 week was given for 15 years, causing development of secondary sexual characteristics and regular vaginal bleedings. The height increased to 142 cm.

Thirty years old she suddenly stopped therapy for 2 weeks. Treatment was again started but no bleeding occurred. Three months later she was pregnant, and the gestational age was estimated to 14 weeks by vaginal examination and ultrasound scanning. Repeated determinations of the oestriol excretion (Frandsen 1963) showed normal values of 2.5–3.8 mg/24 h. In the 26th week of gestation she had a spontaneous abortion elsewhere. The foetus was of female sex, stillborn, macerated and hydrocephalic. It weighed 600 g and measured 34 cm. No tissue could be obtained for chromosome analysis.

Later an exploratory laparotomy was performed. A normal sized uterus, a right gonad, measuring 0.5 x 0.5 x 2.5 cm with a cyst 1.5 cm in diameter and a left normal
Fig. 1.
Ovarian biopsy from the patient with Turner's syndrome (45,XO) showing two early follicles and an atretic follicle (H-E, ×182).

looking ovary, measuring 1.0 x 1.0 x 2.0 cm was found. Step sections of representative biopsies from both ovaries revealed a normal ovarian stroma with only 2 early primary follicles and a few atretic follicles, but no follicles in further development (Fig. 1).

Stimulation therapy with human menopausal gonadotrophin (HMG, Humelog®) was started 7 months later. In spite of a total dose of 2700 IU HMG during a period of 16 days, no increase in the urinary excretion of total oestrogens was seen. The excretion was about 20 ng/24 h.

Substitution therapy with oestradiol 2 mg daily for 3 weeks combined with norethisterone acetate 1 mg daily for 1 week was then initiated: 3 months later the patient stopped treatment for 2 months. She then took a few tablets and stopped again. Ten weeks later she was again pregnant. She was admitted and stayed in our department until delivery.

The patient was followed by weekly determinations of the serum concentration of progesterone (Johansson 1969) and human placental lactogen hormone (HPL) (Nørgaard-Pedersen & Gæde 1973) and by the urinary excretion of oestriol during the whole pregnancy (Figs. 2, 3 and 4). It appears that the progesterone and oestriol values were within the normal range during the whole pregnancy, whereas the level of HPL was rather high and normally increasing until the 29th week of gestation, but stationary after that time. Because of hydramnion amniocentesis was performed in the 28th week. The concentration of $\alpha_1$-foetoprotein in the amniotic fluid was normal, and
Fig. 2.
Serum progesterone levels during pregnancy in the patient with Turner's syndrome (45,XO). The shaded area indicates the normal range.

The foetal chromosome complement was 46,XY. Ultrasound scanning did not reveal any malformations. Caesarean section was performed in the 38th week because of the stationary levels of HPL and a suddenly falling serum progesterone indicating an insufficient function of the placenta, and a normal boy (46,XY) of 2900 g was de-

Fig. 3.
Serum HPL levels during pregnancy in the patient with Turner's syndrome (45,XO). The shaded area indicates the normal range.
Fig. 4.
Oestriol excretion during pregnancy in the patient with Turner's syndrome (45,XO).
The shaded area indicates the normal range.

Oestriol excretion during pregnancy in the patient with Turner's syndrome (45,XO).
The shaded area indicates the normal range.

Ovulated. The puerperal period was uneventful except for a very poor milk secretion. The excretion of total oestrogens remained at a very low level (4–6 μg/24 h); 7 months after delivery the patient reassumed the hormonal treatment.

Case 2
M. F., 31 years. Referred to our department when 20 years old because of secondary amenorrhoea. Puberty was normal, and menarche occurred at the age of 15. During the first 3 years the menstrual cycles were regular, but she then developed oligomenorrhoea followed by secondary amenorrhoea. Height: 154 cm, weight: 43.5 kg. She had normal breasts as well as normal pubic and axillary hair. Chromosome analysis on peripheral blood showed a 46,XX complement. She had a high excretion of total gonadotrophins (> 60 MU/24 h) and a low excretion of total oestrogens (< 20 MU/24 h). Thyroid function was normal. Urinary excretion of 17-ketosteroids (17-KS) was only 1.5–2.2 mg/24 h and the excretion of 17-ketogenic steroids (17-KGS) 3.4 mg/24 h. The diagnosis of Addison's disease was established by an ACTH stimulation test showing an increase of only 30–35 per cent in the excretion of both 17-KS and 17-KGS and furthermore by the presence in serum of IgG antibodies reactive with cytoplasmic components of the adrenal cortex.

Because of Addison's disease treatment with cortisone acetate 30 mg and fluorhydro-
cortisone acetate 0.025 mg daily has been given since then. She felt well on this therapy but no bleeding occurred. During the following years the excretion of total gonadotrophins varied from 140–250 MUU/24 h.

Later an exploratory laparotomy was performed. The uterine cavity measured 5 cm, the right and left ovary 2.0 × 2.0 × 3.5 cm. The left ovary contained a cyst, measuring 3 cm in diameter. Step sections of representative biopsies from both ovaries including the cyst showed a follicular cyst, one primordial follicle and one early primary follicle, but no follicles in further development (Fig. 5).

Shortly after the operation treatment with oestradiol 4 mg + oestriol 2 mg daily for 3 weeks with 1 week interval was initiated. On this dose she had regular bleedings for 3 years. Because of moderate oedema and weight gain the dose was then reduced to oestradiol 2 mg + oestriol 1 mg daily. No bleeding occurred during this treatment: 2 months later she was pregnant. The gestational age was estimated to 9 weeks by vaginal examination and ultrasound scanning. She was admitted and stayed in our department from the 12th to 22nd week and again from the 33rd to 36 week. In the meantime she was followed in our outpatient department.

The patient was followed by frequent determinations of serum cortisol and the excretion of free cortisol in urine, and because of a decrease of both values in the 13th week, the daily dose of cortisone acetate and fluorhydrocortisone acetate was increased to 45 and 0.05 mg, respectively. She continued on this dose until delivery. The concentration of serum sodium and serum potassium was normal during the whole

Fig. 5.

Ovarian biopsy from the patient with premature menopause and Addison’s disease showing one primordial follicle and one early primary follicle (H-E × 182).
Fig. 6.
Serum HPL levels during pregnancy in the patient with premature menopause and Addison's disease. The shaded area indicates the normal range.

Fig. 7.
Oestriol excretion during pregnancy in the patient with premature menopause and Addison's disease, who was treated with cortisone acetate and fluorhydrocortisone acetate. The shaded area indicates the normal range.
pregnancy. Figs. 6 and 7 show values of HPL in serum and oestriol in urine. It appears that the serum concentration of HPL increased normally until the 30th week, when a temporary decrease occurred, but the values were still within the normal range. After the 33rd week, however, a constant decrease was observed, and the last two values were below the lower normal limit. Because of the substitution therapy with corticosteroids the oestriol excretion was very low and only slightly increasing during pregnancy. The decrease in serum HPL levels indicated an insufficient function of the placenta. Caesarean section was therefore performed in the 36th week, and a normal girl (46,XX) of 2300 g was delivered. The puerperal period was uneventful apart from lack of milk secretion. Two months after delivery the patient reassumed cyclical treatment with oestradiol 4 mg + oestriol 2 mg daily, and the daily dose of cortisone acetate and fluorhydrocortisone acetate was again reduced to 30 and 0.025 mg, respectively.

DISCUSSION

Singh & Carr (1966) demonstrated that germ cells migrate to the genital ridges in individuals with gonadal dysgenesis, as they found normal appearing ovaries with a normal number of germ cells in 9 embryos and foetuses with the 45,XO complement. Carr et al. (1968) showed later that the gonadal histology in 45,XO newborns may vary from complete absence of germ cells to a normal number. Gonadal dysgenesis may thus be due to a rapid atresia rather than a congenital absence of germ cells in the gonads, but the cause of this atresia is unknown. Some quantitative effect may be acting, and therefore in rare cases, such as in our first case, some germ cells may remain in the ovaries, allowing the patient to have a transitory ovarian function and even to get pregnant (Bahner et al. 1960; Grace et al. 1973; Nakushima & Robinson 1971). Mosaicism is another possible explanation, but we found no evidence of mosaicism by study of five different tissues (Philip & Sele 1976).

The aetiology of premature menopause is also unknown. The possibility that chromosomal anomalies may play a role in the pathogenesis was raised by the discovery of sex chromosomal abnormalities in a few cases reported (Gordon & Paulsen 1967; Molina et al. 1968; Reyes et al. 1976). However, the great majority of patients with premature menopause has normal chromosome complements (Emperaire et al. 1970; Starup & Sele 1973; Zárate et al. 1970). A perhaps more likely explanation is that the normal disappearance rate for oocytes is exaggerated in these patients because of an autoimmune process in the ovaries. Irvine et al. (1968) reported 5 patients with premature menopause associated with Addison’s disease and demonstrated antibodies reactive to theca interna of the ovaries, which seems to support the theory of an autoimmune aetiology to both premature menopause and Addison’s disease.

An interesting point is the possible relationship between the oestrogen treatment and the subsequent pregnancies in the 2 patients here reported. Polansky
& de Papp (1976) have made a similar observation in a 30-year-old patient with premature menopause. Our patient with Turner’s syndrome was stimulated with 2700 IU HMG without any response. The explanation might be that addition of exogenous gonadotrophins to already tonically elevated endogenous gonadotrophins does little to stimulate the follicle maturation. In contrast, if the endogenous gonadotrophin levels are decreased by administration of exogenous oestrogens, the rebound effect on the gonadotrophin levels following cessation of treatment might possibly trigger maturation and even ovulation. Another and perhaps even more likely explanation is that the oestrogen treatment enhances the response of follicles to FSH and causes an increased receptor content for both FSH and LH as it has been shown in rat experiment by Richards et al. (1976).

REFERENCES

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