SUCCESSFUL PREGNANCY IN A FEMALE PSEUDOHERMAPHRODITE

BY

G. I. M. SWYER, D.M., M.D., D.Phil., M.R.C.P.
Consultant Endocrinologist
Department of Obstetrics and Gynaecology

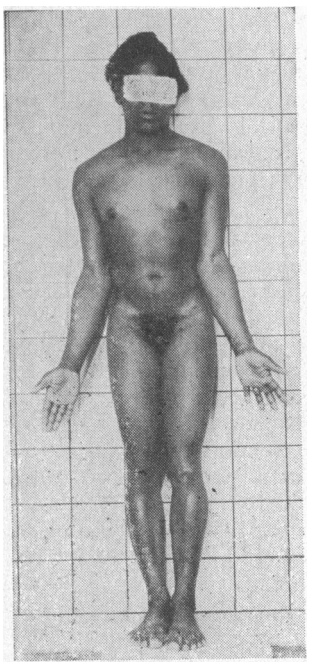
AND

D. G. BONHAM, M.B., B.Chir., F.R.C.S. M.R.C.O.G.
Assistant, Obstetric Unit
University College Hospital, London

Although there have now been several reports of successful pregnancies in women with adrenal disease of different kinds, including Addison's disease, Cushing's syndrome, and adrenal hyperplasia of varying degrees of severity, such pregnancies in female pseudohermaphrodites requiring plastic genital operations (other than mere amputation of the clitoris) are still a rarity. The only report of such a case known to us is that of Gans and Ser (1959). A brief account of the case described below was given (Swyer, 1958) before the patient had conceived.

Case Report

A West Indian negro woman had come to England from Montserrat (Leeward Isles) two and a half years before she was referred to one of us (G.I.M.S.) in November, 1957, at the age of 24, complaining of primary amenorrhoea and abnormalities of the external genitalia. She wanted to get married and wished to know if she could be "made normal." She had five brothers and two sisters—the latter both married with children—all of whom were normal, and she knew of no relatives who had genital anomalies. Her past history was not remarkable.



Photograph of patient before treatment, showing male bodily configuration.

Her height was 5 ft. 0½ in. (136.6 cm.), weight 9 st. 5 lb. (59.4 kg.), and physical examination revealed a male bodily configuration (see Fig.) with wide shoulders, narrow hips, well-developed muscles, and undeveloped breasts. Facial hair was not present, but there were coarse skin pores. Axillary hair was copious and the pubic hair extended upwards over the lower abdomen to the umbilicus. The hair on the limbs was not excessive. The phallus was prominent, measuring 2.5 by 1.3 cm. (1 by ½ in.), and the urethra opened at its base. There were well-developed labio-scrotal folds, but no vaginal orifice could be seen. No inguinal gonads could be palpated. The patient was admitted for investigation.

Investigations. — Urinary 17-ketosteroids (17-KS) 123, 17-ketogenic steroids (17-KGS) 218, pregnanetriol (P'triol) 13.7 and 11.6, pregnanediol (P'diol) 3.5 and 3.1 mg./24 hours; oestrone 16.5, oestradiol 6.1, oestriol 10 μg./24 hours; gonadotrophins approximately 3 mouse uterine weight units/24 hours. Sex chromatin of urinary sediment smear and of neutrophils was positive. After prednisone, 5 mg. q.i.d. for four days, the 17-KS fell to 8.5, 17-KGS to 15.9, and P'triol to 0.2 mg./24 hours. *X*-ray examination after perirenal insufflation showed no evidence of adrenal tumour.

Laparotomy (Mr. D. N. Matthews).—A rather small uterus was seen, together with normal fallopian tubes and ovaries. The adrenals were palpated; the left was slightly enlarged, the right apparently normal in size.

Plastic Operation (Mr. D. N. Matthews).—Incision of the perineum revealed a sizable vaginal cavity which had no communication with the exterior. At the upper end the cervix was palpated. The vagina was dilated and a glass dilator was stitched in position, where it was left for 14 days. The clitoris was amputated, but the glans was retained.

Treatment and Progress

After recovery from the operations, adrenal suppressive therapy was begun on June 25, 1958, with prednisone 5 mg. t.i.d. At that time the 17-KS had risen to 33 mg./24 hours, but two months later they had fallen to 8.4 mg. The first period began 36 days after starting prednisone treatment, and breast changes had already been noticed by the patient. She had now married, and after a short time was able to have effective coitus. The 17-KS fell further to 4.8 mg./24 hours and the prednisone was reduced to 5 mg. b.d. By now she had had menstrual cycles of 34, 28, 32, 28, and 38 days. This last cycle was terminated by prolonged though scanty bleeding which continued for six weeks. The 17-KS rose to 38 mg./24 hours, and she complained of lower abdominal discomfort, dysuria, and malaise. A soft mass was palpable in the abdomen on the left. Pelvic inflammatory disease was suspected and she was admitted to hospital. Examination under anaesthesia (January 20, 1959) failed to reveal any unexpected abnormalities though curettage produced early decidua but no chorion. It was therefore concluded that she had probably had a tubal abortion.

Thereafter she had essentially regular cycles with basal temperatures showing a biphasic pattern, and the 17-KS remaining between 6.3 and 3.6 mg./24 hours, the prednisone dose having been kept constant at 5 mg. t.i.d. After a normal period on September 12, 1959, she had a scanty two-day loss from October 21. Her basal temperature record showed a post-ovulatory plateau continuing from October 1, and a pregnancy diagnosis test was positive on November 5. She was referred to the antenatal clinic but continued to have 17-KS determinations every two months. There was a slight rise, to a maximum of 15 mg./24 hours, at about the fourth month of gestation, but no change in prednisone dosage was found necessary.

The pregnancy progressed uneventfully and she was admitted on June 12, 1960, for elective lower-segment caesarean section. This was performed on June 17 with the delivery of a male baby, weighing 6 lb. 14 oz. (3,120 g.) and showing no congenital abnormalities. Lactation was established but the baby was a rather slow feeder; nevertheless its weight on discharge had risen to 7 lb. 2¾ oz. (3,255 g.). It has continued to thrive and at 20 weeks weighed 14 lb. 8 oz. (6,580 g.).

To cover the stress of delivery, intramuscular injections of prednisolone 20 mg. were given in the evening before operation, and again on the morning and evenings of operation. For the next three days prednisone 10 mg. t.i.d. orally was given, then 7.5 mg. t.i.d. for two days and thereafter 5 mg. t.i.d.

Menstruation was resumed on August 18, nine weeks after delivery, the next three cycles being of 18, 42, and 39 days.

Discussion

From clinical examination it was impossible to tell whether this patient was a male pseudohermaphrodite with abdominal testes, hypospadias, and a bifid empty scrotum or a female pseudohermaphrodite with congenital adrenal hyperplasia. The absence of marked

hirsutism seemed to argue against the latter, though from other points of view this seemed to be the most probable diagnosis. The findings on investigation soon settled the point: the very high 17-KS and 17-KGS and the elevated P'triol and P'diol pointed convincingly to adrenal hyperfunction, while the prompt response to prednisone suppression ruled against an adrenal tumour. The sex chromatin indicated female genetic sex, and laparotomy confirmed the existence of normal internal genitalia. Mr. Matthews found the construction of an effective vagina more straightforward than had been expected; incision of the perineum, dilatation, and the insertion of an indwelling dilator were all that was required and grafting was not necessary. It was an advantage that the patient married soon after, and fortunate that she was able to establish normal coitus with little difficulty.

The basis for the treatment of adrenal hyperplasia with suppressive corticosteroids, following the pioneer work of Lawson Wilkins and his colleagues, is now too well known to require discussion. It is, however, very striking that, even though the patient was 24 years old, her menarche occurred only 36 days after starting definitive prednisone therapy and fertility was established soon afterwards. This dramatic response in patients with severe congenital adrenal hyperplasia is uniformly seen and is, of course, extremely gratifying.

The smooth course of pregnancy, with only a minimal rise in 17-KS excretion, necessitating no change in prednisone dosage other than the prophylactic increase at the time of delivery, was perhaps rather unexpected though none the less pleasing. In the same way the good recovery from the caesarean section, the birth of a healthy baby, the establishment of lactation, and, more recently, the re-establishment of menstruation, have all been a source of great satisfaction.

Summary

A case of female pseudohermaphroditism due to congenital adrenal hyperplasia is described. This 24-year-old patient had primary amenorrhoea and no external vaginal orifice. The surgical construction of an introitus with dilatation of the vagina, and treatment with prednisone, led to the establishment of normal menstruation. She had what was concluded to have been a tubal abortion, followed, six months later, by a normal pregnancy. This proceeded uneventfully, and at 39½ weeks a male baby was delivered by elective caesarean section. Lactation was established, the baby thrives, and, more recently, menstruation has been re-established.

It is a pleasure to record our thanks to Mr. D. N. Matthews for carrying out the plastic surgery on this patient.

REFERENCES

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During 1960, 10,427 deaths in London were reported to the coroner; 1,694 inquests and 8,733 inquiries without inquest were held into deaths; 536 cases of suicide were investigated, compared with 522 in 1959 and 557 in 1958. Of the 536 cases, 156 were of persons over 60 years of age. Four verdicts of murder were returned compared with 13 in 1959 and seven in 1958. Sixteen deaths were caused by chronic alcoholism compared with 23 in 1959 and 22 in 1958.

USE OF CORTICOSTEROIDS IN INFERTILITY ASSOCIATED WITH HIRSUTIES AND OLIGOMENORRHOEA

BY

DAVID FERRIMAN, D.M., M.R.C.P.
Physician, North Middlesex Hospital, London

ANTHONY W. PURDIE, M.B., F.R.F.P.S. F.R.C.O.G.
Senior Obstetrician and Gynaecologist, North Middlesex Hospital, London

AND

W. J. TINDALL, M.D.
Clinical Assistant, Gynaecological Department, Royal Free Hospital, London

Congenital adrenal hyperplasia, caused by enzyme defects in the synthesis of cortisone, classically presents with prepubertal hirsuties, failure of breast development, and primary amenorrhoea. In this form at least, it is a rare disease. A much commoner clinical syndrome is that which presents after puberty with hirsuties, oligomenorrhoea, and infertility. It probably has a multiple aetiology (Ferriman, 1960). It may be due to a primary ovarian anomaly, to congenital adrenal hyperplasia of mild degree, or to a simple constitutional variant involving increased secretion of adrenal androgens. Certainly an adrenal factor appears to be concerned in an appreciable number of cases. Although 17-ketosteroid excretions may be normal, chromatographic separation shows that adrenal androgen secretion is frequently increased (Du Toit, 1951; Gardner, 1953; Johnsen, 1956; Perloff *et al.*, 1957; Gallagher *et al.*, 1958; Prunty *et al.*, 1958; Bush and Mahesh, 1959). Pregnanetriol excretion, another indicator of adrenal activity, is also raised above normal (Nabarro and Moxham, 1957; Gold and Frank, 1958; Prunty *et al.*, 1958).

It is now generally accepted that most of the disturbances in congenital adrenal hyperplasia may be corrected by the use of cortisone, and pregnancies have been reported (Wilkins *et al.*, 1955; Yamashita and Kozakae, 1956; de Alvarez and Smith, 1957; Wilson and Keating, 1958). It was reasonable, therefore, for its effect to be tried in the commoner clinical group of cases with which this paper is concerned, and a number of reports now indicate correction of both menstrual disturbance and infertility in a significant proportion (Jones *et al.*, 1953; Jones and Jones, 1954; Greenblatt *et al.*, 1956; Gold and Frank, 1958; Jefferies, *et al.*, 1958; Wilson and Keating, 1958; Jefferies and Levy, 1959).

This paper reports on a further group of patients with this condition.

Material and Methods

Altogether eight patients have been under study. Seven of these have fallen pregnant while under treatment with corticoids, and six have successfully borne children. One has failed to conceive.

A method of hair-scoring to be described by Gallwey and Ferriman (in preparation) has been used in six members of the group. The "hormonal" score has been found clinically useful, a score above 5 being regarded as unusual to the point of hirsuties. Marital