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ADDISON'S DISEASE AND PREGNANCY

A CASE REPORT

I. D. Huskisson, M.B., Ch.B., F.C.P. (S.A.), M.R.C.P. (Edin.) and C. J. T. Craig, M.D., M.R.C.O.G., *Cape Town*

The patient, a White female aged 26 years, presented on 5 November 1963 during her first pregnancy.

PAST HISTORY

At the age of 14 years the patient developed intermittent attacks of malaise, weakness and vomiting. Between attacks she was perfectly fit, but she had noticed increased pigmentation of the skin.

At the age of 16, when she was Junior Western Province Swimming Champion, she presented in an Addisonian crisis. This followed 2 days of severe malaise, weakness and vomiting. She was admitted to Groote Schuur Hospital, stuperose, dehydrated and with no recordable blood pressure. She had dark patches of buccal pigmentation and generalized skin pigmentation. The biochemical features all supported the clinical diagnosis of Addison's disease. She responded well to intravenous cortisone therapy.

Following this she was very well maintained on cortisone, 37½ mg. a day. Later, 9-alpha-fluro-hydrocortisone was added and the cortisone dosage decreased. The pigmentation decreased and that of the tongue disappeared completely. At the time of conception the patient was very well controlled on a daily maintenance dose of 10 mg. of hydrocortisone and 0·1 mg. of 9-alpha-fluro-hydrocortisone per day.

In 1960 the patient underwent an appendicectomy without ill-effect.

Menstrual history. Menarche, at the age of 13 years. Cycle 6/31 day type and regular.

Marital history. The patient had been married for 3 years. Contraception was not practised.

PRESENT HISTORY

Last menstrual period, 13 September 1963. Estimated date for delivery, 20 June 1964.

Apart from the presenting symptom of amenorrhoea, the patient had noted relatively severe morning sickness as well as nausea and vomiting at other times during the day. This symptom had been present for 10 days. She had noted fullness of the breasts, but had not been troubled by frequency of micturition.

On Examination

General:	Darkly pigmented with a generalized distribution of the pigmentation.
Breasts:	Firm with darkly pigmented nipples and areolae.
Weight:	106 lb.
Blood pressure:	120/90 mm.Hg.
Urine:	No abnormal constituents.
Haemoglobin:	15 G/100 ml.
Vaginal examination:	Confirmed that the patient was pregnant, the uterus conforming to the size of a 6 - 8 week pregnancy.
Papanicolaou smear:	Grade 1—normal.
Blood group:	Ab.Rh.Positive.
VDRL:	Negative.

MANAGEMENT

Antenatal Management

It was concluded that the nausea and vomiting was related to the pregnancy rather than to any loss of control of the Addison's disease. Trifluoperazine, 1 mg. *t.d.s.* and dietary measures were prescribed. The response was immediate and satisfactory.

The patient was thereafter seen at 2-weekly intervals till she was 33 weeks pregnant, then at weekly intervals. At no time during the pregnancy were abnormal constituents detected in the urine and the total weight gain was 22 lb. At the 34th week the foetus presented as a breech and was corrected to a vertex presentation by external cephalic version. There was no evidence of cephalo-pelvic disproportion. The haemoglobin level at term was 14·5 G/100 ml. The blood pressure remained fairly constant until 9 June 1964 when a fall in the diastolic pressure of 10 mm.Hg was noted. As this fall was associated with an increase in the pigmentation and a tachycardia, the maintenance dose of hydrocortisone was increased to 20 mg. per day. The response was satisfactory.

Management of Labour

At 4 p.m. on 27 June 1964, i.e. term plus 6 days, the patient reported a small leak of liquor amnii. Contractions did not follow. On 28 June 1964 the drainage of liquor amnii was confirmed. At 12 noon the cervix was digitally stretched, the membranes were stripped from the internal os, and the forewaters were drained after a low rupture. At 1 p.m. contractions commenced. Pethidine, 100 mg., was given on 2 separate occasions for analgesia. On both occasions the blood pressure was taken at 5-minute intervals for 1 hour, but no fall was noted. Otherwise the blood pressure was recorded throughout labour and for the first 6 hours after delivery at 15-minute intervals. At all times a satisfactory blood pressure was recorded. At 1 a.m. on 29 June 1964, the patient expressed a wish to bear down. A pudendal nerve block with 30 ml. of 1% lignocaine was performed. A right medio-lateral episiotomy was performed. At 1.30 a.m. there was the spontaneous vertex delivery of a living male infant weighing 6 lb. 15 oz. The Apgar rating was 10/10. The only odd feature noted was that the baby had a tachycardia of 200/minute. This settled down rapidly, and when the infant left hospital his condition was perfectly satisfactory.

On the first postpartum day the patient had one isolated temperature reading of 101°F. She was given tetracycline, 250 mg., 6-hourly for 4 days. The rest of the puerperium was uncomplicated, the temperature settling within 24 hours.

The infant was entirely breast fed for the first 4 weeks of life and was partially breast fed for a further 4 weeks.

Replacement therapy during labour and the early puerperium was by means of intramuscular hydrocortisone acetate as follows:

Once labour was definitely established, the patient was given 50 mg. of hydrocortisone intramuscularly. This was repeated 6 hours later, which was one and a half hours before delivery. As soon as the delivery was complete, the patient received a third dose of 50 mg. and 6 hours later a final 50 mg. completed a total dosage of 200 mg. in 24 hours. Over the following 24 hours the patient received 25 mg. 6-hourly and was then put on oral therapy, and by 72 hours after delivery was back on her maintenance dose of hydrocortisone and 9-alpha-fluro-hydrocortisone. The most important guide to adequate control during labour and the early puerperium is frequent checks on the blood pressure. In this case, a satisfactory blood pressure was maintained at all times.

Postnatal Examination

This was performed on 13 August 1964. The mother was well. The pigmentary changes were definitely lighter. The genital organs were fully involuted and the episiotomy was well healed. The maintenance therapy for the Addison's disease was the same as that given before the pregnancy. Contraceptive advice was sought. One of us (C.J.T.C.) has first-hand knowledge of a patient with Addison's disease whose control was completely lost while taking an oral contraceptive, and for that reason this patient was advised to use an alternative measure.

DISCUSSION

In 1958 Kirk[1] reported that about 60 cases had been recorded of pregnancy in association with Addison's disease. It is probable that there are now in addition many more unrecorded cases since the association is being seen with increasing frequency owing to the better steroid maintenance therapy available. Before the advent of the corticosteroids, the association of pregnancy and Addison's disease was uncommon and carried a high maternal and foetal mortality, the latter being mainly due to abortions.

Fitzpatrick[2] reported in 1922 on 11 cases recorded in the literature up to that time and mentioned a 12th case that he had managed in which the diagnosis had been made during the puerperium. All of these patients died during pregnancy or very soon thereafter.

Brent[3] (1950) found a 35% mortality among the 39 recorded cases up to 1946.

Rolland *et al.*[4] (1953) noted that at the Simpson Memorial Pavilion, Edinburgh, only 2 cases had occurred in 60,000 deliveries, while Francis and Forster[5] (1958) found only 1 case in 80,000 deliveries over a period of 42 years at the Liverpool Maternity Hospital. As far as we are aware, the case reported here is the first in Cape Town and possibly the first in South Africa.

Browne and Browne[6] state that the maternal mortality has fallen from 50% to 20% since the introduction of steroids.

The critical times in the management of patients presenting with pregnancy in association with Addison's disease are:

(*a*) In the fist 3 months of pregnancy when the nausea and vomiting may make control difficult. The case reported by Kirk[1] was diagnosed during pregnancy when she presented as a severe 'hyperemesis gravidarum'.

(*b*) At the time of delivery when the increased stress demands an increased dosage of steroids. This is felt to be the most vital stage. It is important that such therapy is given parenterally because there is delayed absorption from the gastro-intestinal tract during labour. If the intramuscular route is used, an absorption peak is reached in 6 to 10 hours, and if urgent therapy is required, the intravenous route is needed.

(*c*) With the development of any obstetric complication, such as postpartum haemorrhage or the need for a caesarean section.

Apart from the stress of labour itself, the use of analgesia and general anaesthesia may provoke a sudden collapse. O'Sullivan[7] reported a case in which sudden death occurred after an intravenous injection of morphine sulphate. This patient had also had a postpartum haemorrhage. Pethidine would seem safer to use than morphine, but should not be combined with chlorpromazine or promazine since such combinations may produce profound hypotension in susceptible patients. Although general anaesthesia may produce collapse, Sluder[8] in 2 cases and Allahbadia[9] in 1 case performed elective forceps deliveries under general anaesthesia. We feel that where forceps or other manipulative deliveries may be indicated, local anaesthesia would be safer. However, Papper and Cahill[10] suggest that patients with Addison's disease tolerate analgesics and anaesthetics normally if they receive adequate substitution therapy.

Francis and Forster[5] feel that caesarean section must be avoided as far as possible because of the summation of surgical and obstetrical risks. They quote the records of only 1 patient who was successfully delivered by caesarean section and this was with the use of cortisone.

There are 2 views concerning the possible role of the foetal adrenal gland and the placenta in the production of steroid hormones which might become available to the mother. Jailer and Knowlton[11] reported on 1 case where they were able to extract from acetone-dried placental tissue a substance with an ACTH type of activity. They suggested that the placenta was the source of adrenal cortical hormones and accounted for the increase of 17-ketosteroid excretion that they were able to record during pregnancy in their case. Francis and Forster[5] have suggested that the placenta has some mineralocorticoid activity and hence the administration of mineralocorticoids by mouth can be reduced in the last trimester. Browne and Browne[6] have also noted that the maintenance dosage required may be lessened by the sodium-retaining effects of the placental hormones and of foetal cortical activity. Moore and Freeman[12] have reported on a case that showed dramatic improvement in the last trimester of pregnancy. Sluder[8] has reported on 2 cases showing definite decrease of pigmentation in the second half of pregnancy.

Gabrilove and Schval[13] express the opposite view—that there is no real evidence to suggest that the Addisonian patient improves spontaneously during pregnancy. 'It is doubtful if the foetal adrenal cortex or the placenta secrete biologically significant amounts of adrenal corticosteroids with respect to protection of the pregnant Addisonian from crisis'. Laidlaw *et al.*[14] concluded from studies of pregnancy in 2 patients who had had bilateral total adrenalectomies, that the amount of aldosterone rise was no more than one-tenth of the average excretion by normal pregnant women in the third trimester. 'Certainly the major source of urinary aldosterone during pregnancy must be sought outside placenta and foetal adrenal'. In the case presented here, the Addison's disease showed, if anything, a slight deterioration during the later months of pregnancy, and we felt that in the presence of satisfactory control of Addison's disease and in the absence of evidence of fluid retention, a reduction in steroid therapy was not indicated. Singh[15] has also reported on 1 case in which the skin pigmentation increased near to term and decreased in the puerperium. This patient required increased dosage in the later months of pregnancy.

There is no longer any controversy about the position of therapeutic abortion. Patients with Addison's disease can be allowed to undergo pregnancy and delivery without any enhanced risk, provided they are carefully

assessed and controlled. Adequate control in patients with Addison's disease appears (*a*) to enhance the fertility, (*b*) to reduce the risk at the time of delivery and (*c*) to improve the prospects of successful breast feeding.

SUMMARY

A case is presented of a 26-year-old patient known to have Addison's disease who became pregnant.

Careful antenatal and intrapartum supervision by both physician and obstetrician ensures that the patient has the best chance of a successful outcome.

We should like to express our thanks to our colleague, Dr. R. Maggs, paediatrician, for his care of the infant at the time of birth and in the first week of life.

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EXTENSION OF CERVICAL CANCER TO THE SUPERFICIAL INGUINAL LYMPH NODES

DERK CRICHTON, M.B. (CAPE TOWN), D.PHIL. (OXON.), F.R.C.S.E., F.R.C.O.G., *Head of the Division and Professor of Gynaecology and Obstetrics, King Edward VIII Hospital and University of Natal*

The possibility of extension of cervical cancer to the superficial inguinal lymph nodes usually passes unrecognized in standard textbooks on gynaecology, and even the most recent monographs on cervical cancer merely make passing reference to such a possibility in advanced cases. None attempt an estimate of frequency of this complication in their live patients, and the incidence reported in necropsy studies is very variable.

During a phase of special interest in the accuracy of execution of necropsies I formed the impression that spread to the superficial inguinal lymph nodes occurred in a higher percentage of cases than was currently thought to be the case. This stimulated the present study in which superficial inguinal lymph node biopsies were taken as a routine procedure from all patients suffering from cervical cancer before administering treatment, with the object in view of ascertaining the incidence and possible significance of this direction of spread.

DETAILS OF THE INVESTIGATION

The series consists of 591 patients—subsequently proven to have cervical cancer on histological examination of biopsy specimens taken from their cervices. A clinical decision as to whether the superficial inguinal lymph nodes were benign or malignant was made in each case before taking samples for biopsy from superficial inguinal lymph nodes under anaesthesia, and proceeding to perform the remainder of the routine investigations of patients suspected of having cervical cancer. These investigations included clinical assessment of the stage of the growth, biopsy of the cervix, cystoscopy, proctoscopy, and in many instances the biopsy of tissue taken from the bladder and rectum.

RESULTS

Among the patients assessed clinically as having stage I cervical cancer, malignant spread to the superficial inguinal lymph nodes was not found (0 out of 36 cases); but malignant superficial inguinal lymph nodes were found in 5·1% of stage II growths (7 out of 136 cases); in 5·2% of stage III growths (10 out of 193 cases) and in 14·1% of stage IV growths (32 out of 226 cases).

Malignant superficial inguinal lymph nodes were discovered on the right side in 35 instances, the left side in 47 instances, and there was bilateral carcinomatous involvement in 28 instances.

The 'clinical' accuracy of deciding whether the superficial inguinal lymph nodes were benign or malignant was also assessed. In the group of 49 cases with malignant superficial lymph nodes they were regarded as 'clinically' benign in 30% of cases (15 instances). Among the 370 cases with stage III and stage IV growths, in whom the lymph nodes were proved to be benign on histological examination, a previous 'clinical' diagnosis of malignant inguinal lymph nodes had been made in 13% of cases (58 instances). The error was greatest in stage IV growths.

It is important to appreciate that no inguinal lymph nodes whatever were palpable clinically in some fat patients until the inguinal lymph nodes were explored digitally through overlying skin incisions, and histological examination of the lymph nodes discovered in this way proved them to be malignant in 2 instances.

Biopsy of the superficial inguinal lymph nodes did not predispose to subsequent malignant ulceration in the groin, even when the inguinal lymph nodes were found to be malignant. Paradoxically the single case which presented with recurrent cancer ulcerating extensively in the left groin (Fig. 1) was a case omitted from the series, because biopsy on a superficial inguinal lymph node was performed only on the 'contralateral' side. Usually patients who died of cervical cancer did not experience a pronounced increase in the size of inguinal lymph nodes which had been established to be malignant.

The extent of spread of cervical cancer down the vaginal wall had a pronounced influence upon the likelihood of spread to the superficial inguinal lymph nodes (Table I); thus, when less than one-third of the vagina was involved,