

Hypophysectomy for Diabetic Retinopathy During Pregnancy

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SUMMARY

A clinical account is given of a patient with diabetes for twenty-one years, suffering from proliferative diabetic retinopathy, in whom hypophysectomy was performed in the eighth week of pregnancy. The pregnancy proceeded uneventfully, apart from the development of hydramnios; the patient was delivered at the thirty-seventh week by cesarean section. Regression of the retinopathy was noted to commence during the pregnancy and has continued since delivery. Insulin requirements increased by 30 per cent during pregnancy. The baby showed none of the features commonly seen in the infants of diabetic mothers. *DIABETES* 21:972-75, September, 1972.

A clinical account is given of a patient who was diabetic for twenty-one years and eight weeks' pregnant when hypophysectomy was performed for the treatment of proliferative diabetic retinopathy. This would appear to be the first report of hypophysectomy undertaken during pregnancy in a diabetic patient.

CLINICAL SUMMARY

Mrs. J. S. developed diabetes mellitus with classical symptoms at the age of six, in 1948. Control was established with diet and insulin. During the next ten years she lived in the country away from close medical supervision; the control of her diabetes was poor despite the use of a variety of insulin regimes. She had had one episode of diabetic ketosis during this time.

When reviewed in 1958 she was being maintained on a mixed injection of Semilente insulin (IZS amorphous) 36 U. and Ultralente insulin (IZS crystalline) 72 U. daily. She appeared physically well and was without clinical evidence of diabetic vascular disease. Her regimen was changed to Semilente insulin b.d., 38 U. a.m. and 32 U. p.m. with improved control.

In 1962 at the age of twenty-one, having had diabetes mellitus for fourteen years, routine examination revealed the presence of a few microaneurysms in the right eye. The blood pressure was 120/80 and traces of albumin were noted fairly consistently on urinalysis. At her request insulin was altered

to Lente insulin (IZS) alone and fair control was maintained on 72 to 80 U. a day as judged by random blood and urine sugar tests.

Shortly after her marriage in 1966 she had an episode of severe diabetic ketosis associated with a urinary tract infection. When seen following this episode, extensive retinopathy with small scattered hemorrhages, microaneurysms and a few small exudates was noted in both eyes. The only other abnormal finding was the bilateral absence of arterial pulsation below the knee. The blood pressure was unchanged.

Over the next two years she remained well apart from recurrent urinary tract infection and a suspected abortion after eight weeks' amenorrhea. The retinopathy progressed with proliferative changes and fresh hemorrhages in both eyes, particularly the right. Vision remained unchanged however, R, 6/12-6/18, L, 6/9-6/12, and the blood pressure and proteinuria were unaltered.

In November 1968 she suffered a vitreous hemorrhage in the right eye and the vision in this eye has since been reduced.

Because of the rapid progression of the retinopathy, hypophysectomy was considered at this time and investigations were undertaken to assess the suitability of the patient for the performance of this procedure. Blood urea was 32 mg./100 ml., serum creatinine 0.7 mg./100 ml. and creatinine clearance 54 ml./min. The electrocardiograph was normal. A pregnancy test performed because of amenorrhea of four months' duration was negative. Lente insulin 72 U. daily, with a diet containing 180 gm. of carbohydrate, maintained satisfactory control of the diabetes.

In December 1968 trans-sphenoidal hypophysectomy was attempted but the operation was abandoned because of severe hemorrhage and she was readmitted to hospital for trans-frontal hypophysectomy in January 1969. Her general condition remained unchanged. Because of the persistence of amenorrhea the pregnancy test was repeated and on this occasion was positive. As the original indications for hypophysectomy remained, a trans-frontal operation was performed after full discussion with the patient and her husband.

Postoperatively she developed diabetes insipidus. The diabetes mellitus became restabilized on 40 U. of Soluble insulin given in divided dosage. Blood urea and serum creatinine were unchanged and creatinine clearance rose from the pre-operative level of 54 ml./min. to 90 and 102 ml./min. It is apparent thus that the pregnancy-induced rise in creatinine clearance exceeded the effect of hypophysectomy in reducing clearance. Nonetheless the levels recorded during this pregnancy were not as high as commonly seen. These suboptimal levels could have been due to the hypophysectomy or to some impairment of renal function consequent upon the long-

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standing diabetes. Serum thyroxine fell from 4.0 $\mu\text{g.}/100$ ml. to 2.5 $\mu\text{g.}/100$ ml. Replacement therapy consisted of cortisone acetate 12.5 mg. t.i.d., thyroxine 0.2 mg. daily and pitressin tannate 5 U. at two to three-day intervals as required.

At this stage she was transferred for obstetric care to the Royal Women's Hospital and when first seen on Feb. 19, 1969 it was assessed that she was eighteen weeks' pregnant. The pregnancy proceeded uneventfully with a slight increase in insulin requirement and with normal urinary estriol levels as shown in table 1. Endocrine replacement therapy was unchanged. At thirty-two weeks she was admitted to hospital for observation following an episode of vomiting and X ray showed evidence of hydramnios with estimated fetal maturity of thirty-one to thirty-two weeks. At this time the blood pressure was 135/80, the urine contained no protein and creatinine clearance was 101 ml./min. Elective cesarean section was performed on July 5, 1969 when it was estimated that she was thirty-seven weeks' pregnant. A male child weighing 2,930 gm. was delivered. There was no lactation after delivery.

Following delivery her insulin requirements fell rapidly and she was restabilized on Lente insulin 32 U. daily. Before discharge a provocative hypoglycemia test was performed using 12 U. of Soluble insulin intravenously. Blood sugar fell from 43 mg./100 ml. fasting to 27 mg./100 ml. at sixty minutes and 13 mg./100 ml. at ninety minutes with severe hypoglycemic symptoms. The basal level of plasma immunoreactive growth hormone estimated by the method of Jacobs¹ was less than 1.0 ng./ml. and did not rise following this stimulus.

The baby at delivery had an APGAR Rating of 2. Regular respirations were established at four minutes and at five minutes the APGAR rating had risen to 8. The attending pediatrician commented that the baby "did not look typically edematous." Subsequent progress was good. Mild hypoglycemia occurring in the first forty-eight hours was readily managed by routine methods. No signs of respiratory distress were evident. Oral glucose tolerance (1.0 gm./kg.) performed on the eleventh day gave the following result:

Minutes	Fasting	30	60	90	120	150	180
mg./100 ml.	23	46	45	44	37	38	33

The patient has been followed for eighteen months since delivery. Her diabetes remains stable but insulin sensitive requiring Lente insulin between 20 to 24 U. daily. Replacement therapy with cortisone acetate 12.5 mg. t.i.d., thyroxine 0.2 mg. daily has been continued along with chlorthiazide 0.5 b.d. and lysine vasopressin spray as required for the control of diabetes

insipidus. She remains well, managing both her house and child and a part-time job. The vision in the blind right eye is unchanged but that in the left eye has improved to 6/6 with striking regression of the reversible diabetic changes in the retina. These were observed to be regressing throughout the pregnancy and in particular new vessels began to diminish, and no new hemorrhages were noted during close ophthalmological observation. Twelve months after hypophysectomy the ophthalmological report of the left eye was that no obvious hemorrhages or new vessels were to be seen but some lateral scarring and gliosis was present. When last seen twenty-eight months after hypophysectomy there was no evidence of fresh hemorrhages or microaneurysms but narrowed vessels and gliosis remained. The baby remains well with no evidence of any congenital abnormality.

DISCUSSION

Caird² has reviewed reports of the influence of pregnancy on the course of diabetic retinopathy. In the case of simple retinopathy there is considerable difference of opinion, some authors suggesting that the risk of progression is high and others that it is low. Fewer accounts of the course of proliferative retinopathy exist. In general it seems that there is a higher risk of deterioration during pregnancy of this type. In a study currently being undertaken, all five patients suffering proliferative retinopathy at the beginning of pregnancy have shown signs of deterioration.³ Thus the amelioration of retinopathy observed in this patient during pregnancy would have been due to the hypophysectomy rather than to spontaneous change.

The decision to offer hypophysectomy to this patient for the treatment of rapidly advancing proliferative retinopathy was based on the observed natural history of her eye disease, her youth, and her generally good clinical condition with particular reference to her vascular status. It was appreciated that she had some albuminuria and that creatinine clearance was reduced but the serum creatinine level was normal as was blood urea. Retinal photocoagulation, yet a controversial form of treatment,

TABLE 1
Indices of progress throughout pregnancy

Duration of pregnancy—weeks	21	24	27	31	32	33	34	35	36
Soluble insulin dose a.m./p.m.	24/16	28/20	32/20	32/20	28/20	24/24	24/24	28/24	28/24
24-hour urine estriol (mg.)		3.6	4.3	12.6	17.2	17.5	23.2	19.8	27.2
Blood sugar mg./100 ml.	Fasting	325	280	310	175	125	90	154	125
	11 a.m.	160	240	215	290	55	130	131	110
	3 p.m.	140	245	185	230	115	165	157	167
Blood urea mg./100 ml.	20			26				26	

was not available at that time as an alternate therapeutic consideration.

There are few reports of hypophysectomy in pregnancy in the human. Little⁴ et al. and Kaplan⁵ have reported continuation of pregnancy after hypophysectomy in two patients at twenty-six and twelve weeks respectively. In each instance there was evidence that an effective hypophysectomy had been performed because both patients were dependent on replacement therapy. In an additional unreported case in our care an effective trans-frontal hypophysectomy was performed at the twenty-sixth week for the treatment of disseminated thymic carcinoma, the pregnancy continuing uneventfully. Delivery of Kaplan's case and the patient described in this report was by cesarean section but the other two patients delivered vaginally after the spontaneous onset of labor. The present report appears to be the first of a diabetic to undergo hypophysectomy during pregnancy.

Following hypophysectomy in each of the above four patients there was clinical and laboratory evidence of diabetes insipidus requiring continuous replacement therapy. Despite this evidence of substantial damage to the hypothalamic-posterior pituitary system, in three, uterine contractions occurred and two had normal vaginal births. A similar situation occurs in isolated diabetes insipidus of either familial or idiopathic etiology and raises some doubt as to the role of oxytocin in the initiation and progress of parturition. However, it is possible that hypophysectomy did not interfere with oxytocin secretion and release by the hypothalamus. Electrophysiological studies in animals provide some evidence for the differential susceptibility of oxytocic and antidiuretic functions to localized hypothalamic damage.⁶ Although these references to the co-existence of diabetes insipidus and pregnancy are made in relation to this patient and to the reports of others, hypophysectomized in pregnancy, it is well recognized that satisfactory ablation of anterior pituitary function can be achieved without the development of diabetes insipidus provided a satisfactorily low stalk section is achieved.

There is considerable species difference in the effect of pituitary ablation on established pregnancy. In the dog, cat, rabbit and ferret, abortion invariably results but in the mouse, rat, guinea pig, monkey and now man the pregnancy continues, although in some the birth mechanism is disturbed. There is some uncertainty as to the time of gestation at which the pituitary can be destroyed without disturbance of pregnancy in each of these species.⁷

The course of the pregnancy in the present patient with insulin-dependent diabetes of long duration and with evidence of microangiopathy was uneventful. The insulin requirement late in pregnancy was 52 U. per day, compared with a prepregnant, prehypophysectomy dose of 72 U. and a postnatal requirement of 20 to 24 U. a day. The commonly observed increase in insulin requirement during this pregnancy would suggest that neither anterior pituitary hormones nor pituitary-dependent insulin antagonists^{8,9} are important determinants. Placental function as judged by urinary estriol levels was normal and it would seem more likely that the placental hormones, chorionic somatomammotrophin (SMT or HPL), progesterone and estrogens are the important insulin antagonists in pregnancy.¹⁰

The infant was born without the features commonly seen in babies born to diabetic mothers, embryomegaly and edema. In light of the variability in diabetic pregnancy of fetal weight and of the occurrence of fetal edema, and of the influence of maternal renal function on these fetal parameters, it is difficult to interpret, relative to the hypophysectomy, the significance in this patient of the absence of these fetal features.

The satisfactory regression of diabetic retinopathy which occurred in this patient following pituitary ablation, began during pregnancy and has continued throughout the subsequent eighteen months' observation. There are varying reports of the results of hypophysectomy and some give favorable accounts of the early response¹¹⁻¹³ while others^{14,15} are less optimistic about the long-term results.

The mechanism by means of which hypophysectomy might induce amelioration of diabetic retinopathy is unknown. Thus the successful remission observed in this patient in the presence of the fetoplacental unit with large amounts of pituitary-like hormones together with progesterone, estrogens and their androgenic precursors is of interest. Obviously the presence of these hormones has not nullified the beneficial retinal effect in this case, associated with the removal by hypophysectomy of their pituitary-dependent counterparts.

The history of this patient operated during pregnancy, lends a new clinical dimension to observations regarding hypophysectomy for diabetic retinopathy but it brings no nearer a precise explanation as to the means by which remission of the retinopathy occurs as a consequence of the procedure.

ACKNOWLEDGMENT

The assistance given by Mr. J. B. Curtis (Neurosurgeon), Dr. R. M. Rome (Obstetrician), Dr. G. Dahlen-

berg (Pediatrician), and Drs. M. Horvath, P. Hardy-Smith (Ophthalmologists) in the management of this patient is gratefully acknowledged.

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