✓ PREGNANCY IN ASSOCIATION WITH DIABETES MELLITUS

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That the problems presented by the association of pregnancy and diabetes mellitus is of absorbing interest is proved by the recent spate of reviews and reports on the subject. Despite this evidence of continuing thoughtful study these problems remain largely unsolved and, in defiance of considerable growth of knowledge, much remains obscure.

The facts are now well known, but the explanation underlying them, together with the best means of meeting them, is in dispute. These facts must bear repetition for the sake of clarity.

Prior to the discovery of insulin the combination was but rarely seen, on two accounts: few young diabetic girls survived to childbearing age; and amenorrhoea and infertility of nutritional or endocrine origin afflicted those who did. With the successes achieved by insulin, and especially since long acting insulins became available, carrying their much improved degree of control, both these influences have been abolished. Nowadays, though diabetic fertility is not up to normal, these pregnancies account for something like one in three hundred. That they are not more frequent depends on the incidence of diabetes mellitus falling most heavily on women past childbearing age.

Some time after insulin came into general use, it became clear that pregnancy in diabetics ran a distinctive abnormal course. Later still the pooling of individual experiences led to widespread recognition of a specific problem, the outstanding features being: for the mother, a liability to toxæmia and to spontaneous premature delivery of an apparently post-mature infant; for the foetus a tendency to die in utero in the last few weeks of pregnancy or in the first two days of neonatal life and in each case to be overweight. Together these made for a stormy pregnancy, a difficult labour and, most important, the persistence of a foetal mortality rate of about 50 per cent., little if any better than that of pre-insulin experience.

The next advance was the recognition that women destined to develop diabetes were subject to identical obstetric and foetal accidents, and that the incidence and severity of these increased as

the date of delivery advanced towards the date of onset of the disease. Thus, in the five years immediately antecedent to the diagnosis of diabetes the foetal death rate equals that of overt diabetics, while in the twenty or more years preceding, it is very much less, yet significantly more than the normal.

Following the facts further, the *influence of the pregnancy on the diabetes* deserves first consideration. Two fundamental changes explain the instability and tendency to the more serious complications often encountered. First, lowering of the renal threshold common to many pregnant women is not only much more common in diabetics, but much more severe towards the end of such a pregnancy. This results a glycosuria out of all proportion to blood sugar levels. Second, there is a steady deterioration of carbohydrate tolerance throughout pregnancy, again most obvious in the last three months and displayed as an increase in insulin needs not accounted for by any increase in carbohydrate intake. These together explain why pregnancy will discover cases of latent diabetes, the aggravation of which, together with disproportionate sugar leak consequent on the lowered threshold, results in glycosuria obvious on routine testing. Further points deserve mention: towards the end of pregnancy there may be a reversal and carbohydrate tolerance tends to improve; even more striking is the sudden drop in insulin requirements during and after parturition, continuing for some days and marking a definite recovery in the diabetic state. Finally, the patient's condition either reverts to her pre-pregnant state or is even better. It can be fairly said that pregnancy alone never accounts for any permanent deterioration in the diabetes mellitus nor is there evidence that the rate of vascular degeneration is augmented.

The precise reason for exacerbation of the diabetic state is not clear. Increased basal metabolic rate may be partially responsible, but since insulin requirements rise before any corresponding rise in this rate can be detected, other factors must be involved. A reasonable suggestion is an exaggeration of anti-insulin effect, and it is tempting to

ascribe this to excessive output of anterior pituitary diabetogenic factor corresponding with the general overactivity of this gland during pregnancy.

The late mitigation of the diabetic state is also open to various explanations. Maternal hyperglycaemia could stimulate over-secretion of foetal insulin but such evidence as there is inclines against this view, insulin not being known to pass the placental barrier. In any case the more striking post-partum improvement remains unexplained. More credible is the view that some harmful influence operating throughout pregnancy is removed with parturition. Anterior pituitary function could be implicated again, as such a harmful influence could well be the diabetogenic factor, the output of which, together with associated growth hormone, could be suddenly suppressed at term to make way for the requisite output of prolactin. No confirmation of this attractive theory is forthcoming and it must remain guess-work.

In a known case the early and late months provide most diabetic complications. Where anorexia, capricious appetite or vomiting manifest in the early months, insulin reactions may be both frequent and severe, and especially so when insulin dosage is based on urinary sugar estimations. In the later months ketosis is the main hazard. Foetal needs for carbohydrate increase, while at the same time renal leakage may account for considerable waste. Unless these factors are allowed for, the mother can be virtually deprived of carbohydrate, and fat is over metabolised with grave consequences. During labour severe hypoglycaemia may again be prominent, contributed to by extra muscular exertion together with spontaneous improvement in the diabetic state.

Lactosuria adds to the problems of diabetic control in late pregnancy and the puerperium, and provides another threat to satisfactory treatment where insulin dosage is estimated against the degree of reducing substances in the urine.

The *influence of diabetes on the pregnancy* is a more serious one and must be accepted as positively harmful. In the early months this is hardly perceptible, the abortion rate being little raised above the normal. Later on it becomes progressively greater, showing in the exceptional rate of toxæmic complications to which these patients are prone, figures quoted ranging from two to fifty times the normal. This diversity of figures depends on the wide scope of the meaning of the term toxæmia, some including minor departures from health, others discarding all but gross evidence in their diagnosis. Common estimates are 25 to 30 per cent. of toxæmia sufficiently serious to arouse concern. Appearing usually after the fifth month it follows the pattern of toxæmia in

non-diabetic pregnancies, the incidence and severity rising steadily in the later months, reaching a maximum in the last four to six weeks.

Hydramnios is a common early sign, presenting as abdominal pain due to the tense and tender uterus and, where substantial, detected by a sudden rise in the position of the fundus. Smaller degrees are difficult to diagnose. Causes are obscure: it may well represent early water and salt retention; as with even the best balanced case of diabetes the blood sugar is intermittently raised, high glucose content of the liquor may be responsible. Oedema, often of sudden onset, hypertension and albuminuria together or separately are other familiar manifestations. Remembering that diabetics are independently subject to vascular degeneration, often demonstrable after ten years' duration, it is no surprise to know that the toxæmia is more frequent and more severe in victims of long standing disease. This connection is stronger where known vascular changes exist in the mother and is strongest where frank hypertension or renal involvement complicate the maternal diabetes.

Unusual presentations are common, though earlier findings of 30 per cent. breech presentation have not been repeated. The uterus is unduly irritable, may exhibit contractions throughout pregnancy and uterine inertia may cause difficulties in labour.

The most impressive evidence of specific abnormality lies in the unusual pattern of natural delivery; either spontaneous premature delivery at about eight months, but recorded as early as the twenty-eighth week, of an infant considerably larger than its expected weight for its age; or stillbirth at term or after of a macerated giant foetus. The placenta falls into line with the general trend to irregularity and of large size, contains many small infarcts suggestive of premature ageing. Lactation is frequently inadequate from endocrine or nutritional causes.

Remarkably, the maternal survival in spite of the added chances of complication of both states is highly satisfactory being often reported as 100 per cent., occasional coma in the unrecognised case and severe hypertension accounting for the few fatalities. This figure contrasts very favourably with the 25 per cent. mortality reported in the pre-insulin era, together with a further 25 per cent. of mothers lost in the two years following childbirth.

The *injurious influence of maternal diabetes on the foetus* is equally striking. Two characteristics stand out: inherently poor viability, leading to an undue proportion of neonatal deaths; an inclination to overweight.

The first, affecting both premature and full term

infants, is demonstrated by a weak cry at birth or after, a sluggish attitude and, predominant in its adverse implication, poor colour, tendency to cyanosis and difficult breathing. These last signs are dependent on pulmonary atelectasis and much speculation has been given as to the origin of this. Either blocking of the upper air passages with mucus, or depressed function of the under-developed brain, or both of these may be involved. Inhalation of amniotic fluid is another possibility as excess has been found in the babies' stomachs. For one or more of these reasons, or for others yet unknown, death in the early neonatal period is a commonplace. Hypoglycaemia, once considered a potent factor, is now regarded as unimportant.

The second characteristic, the large size of the baby, is contributed to by oedema, by excess fat and by exceptional length of body and limbs. More remarkable is the general splanchnomegaly shown chiefly in the large size of the heart, liver and spleen. By contrast the skull and brain are small and islands of erythropoiesis persist in liver and spleen similar to those found in erythroblastosis foetalis.

Lastly, congenital defects add to the causes of death, being found with unexpected frequency.

Labour in any event is likely to be difficult and to impair further the infant's chance of life. Instability of the diabetes and tendency to toxæmia of the mother, premature rupture of the membranes, difficulties attendant on hydramnios, abnormal presentation and delivery of a large baby all share the blame.

Many theories have been advanced in an attempt to explain these matters but none wholly convincing. Thus, maternal hypoglycaemia has not been connected with foetal disaster and hyperglycaemia is equally exonerated since neither the severity of the diabetes nor the degree of its control bears any constant relationship to the general pathology. Raised maternal blood sugar may favour the over-nutrition of the infant as displayed by excessive fat deposits, but alone could hardly account for the large organs and long bones. That it is not the dominant factor in foetal overweight is proved by experience with pre-diabetics whose infants, as has already been said, behave as those of diabetics. Ketosis and coma must add to foetal injury but such episodes are rare and becoming more so under modern careful supervision. Further, many infants are known to have survived maternal ketosis while countless others have died in its absence.

Toxæmia subscribes more to the poor outlook, and 46 per cent. of prematurity and of foetal deaths both, have been recorded in its presence. It is still not the major fault. There is no true correlation between the incidence of toxæmia and

that of foetal morbidity. More convincing is that the foetal mortality of the toxæmic diabetic is at least twice that expected of toxæmia alone.

Duration of the diabetes is one element definitely associated with a high rate of morbidity. Whether this adverse influence of long standing disease is mediated through vascular degeneration or works independently is not settled.

Age at onset plays some part, the young woman whose disease arose in childhood being a notoriously bad subject for a successful outcome, the older woman with diabetes mellitus of recent origin standing a much better chance of having a live baby.

Neither diabetic nor obstetrical influences then separately or jointly account for the known factors. Hence, when the theory of *hormonal imbalance* was put forward it was welcomed in the hope that it would solve the problem. It came into the picture in the following manner. Workers in Boston found that in toxæmia of pregnancy, at about the fifth month, unusually high levels of chorionic gonadotropin persisted in the blood, together with correspondingly low values of oestrogen and progesterone. Later, it was found that the fall in sex hormones preceded the rise in chorionic gonadotropin, the latter being regarded as a compensatory mechanism. This hormonal imbalance preceded any clinical evidence of toxæmia by some weeks and it was claimed that redressing the balance, by administration of the deficient sex hormones, could avert or reduce the toxæmia. Many patients concerned in the original work were diabetics and the principles were accordingly widely applied to the general study of pregnancy in this disease. Ample confirmation was soon forthcoming of the presence of an unusual hormonal pattern in many diabetics. The placenta being the site of origin of the three hormones concerned, the findings were interpreted as representing disordered placental function either idiopathic or resulting from vascular degeneration. Failure to secrete sex hormones is the supposed primary fault, compensatory high output of chorionic gonadotropin acting as the damaging agent in production of maternal and foetal pathology. An alternative view holds that deficient oestrogen levels allow for uninhibited anterior pituitary hyperfunction. A third theory considers the hormonal imbalance to be but a side effect of some unknown fundamental happening itself responsible for maternal morbidity and foetal mortality. If the first or second viewpoint is right, hormone therapy could be expected to be of value; the third belief is incompatible with such a hope.

The great champion of the theory of hormonal imbalance as being the major factor in the irregular

pregnancies is White, who, working in Joslin's world famous clinic, claims that an abnormal course can be predicted on discovery of hormonal imbalance and that replacement therapy with stilboestrol and progesterone can substantially correct this course. Using this method she claims a foetal survival rate of 90 per cent. with maternal toxæmia reduced to 5 per cent. Here are other relevant figures concerning her 513 cases, the biggest number yet observed: of 40 women found to have normal hormonal levels there were 95 per cent. live births, no spontaneous premature deliveries and only two cases of serious toxæmia; of 368 women with the demonstrable hormonal imbalance but treated with both sex hormones there were 90 per cent. live births, eight cases of spontaneous premature delivery and five cases of severe toxæmia; with the 96 women known to have a similar hormonal imbalance but who were not treated, the foetal survival rate was only 60 per cent., while pre-eclampsia affected half the patients and spontaneous premature delivery occurred in eighteen cases. In other hands this therapy has not yielded equally successful results.

Though the existence of such a specific hormonal imbalance is now agreed, the clinical usefulness of replacement therapy is not generally accepted. In fairness it should be said that many foetal death rates show a reduction in recent years to figures between 10 and 20 per cent. This improvement could result through awareness of the risks, with resultant close attention to details of both diabetic control and threatened toxæmia, and to the current practice of timely termination of pregnancy. On the other hand some credit could be given to the now widespread use of sex hormones. Disagreement as to the manner in which the hormones work has caused stilboestrol to be used alone (without progesterone) in the belief that inhibition of a previously over-active pituitary gland is the desired aim.

Management is the concern of physician, obstetrician and paediatrician alike and according to their successful co-operation can good results be expected. Complete agreement exists as to the essential aims. That is: good control of the diabetes; and prevention or amelioration of water retention and other evidences of toxæmia.

Changes in diet and insulin dosage are necessary. Carbohydrate intake should be increased to allow 30-50 grams for the foetus according to its maturity, with a margin for renal glycosuria which if severe can account for 50-150 grams loss of carbohydrate. Thus 180-250 grams are usually needed. Protein intake must likewise be raised to a minimum of one gram for one pound of body weight, two grams being a recommended allowance towards term or where water retention is present.

Fat intake is estimated according to the mother's weight, 20-30 pounds being a suitable total gain. Excessive gain is to be avoided at all costs, yet diabetics are unusually prone to it and very low fat intake is sometimes indicated. Lean patients, provided they have no tendency to ketosis, may take what fat they like. Full supplements of vitamins should be given.

It cannot be stressed too firmly that insulin dosage must be adjusted only with blood sugar guidance, in the face of a low renal threshold with its accompanying deceptive glycosuria. Not only the amount but the type of insulin may need to be changed. Where a patient is accustomed to one injection of mixed soluble and protamine zinc, a substitution of more frequent injections of soluble even up to three or four doses daily may be useful, keeping the protamine zinc dose low. This applies especially where diminished appetite, vomiting or threatened ketosis appear. Needless to say, all refractory cases and those complicated by any but minor degrees of ketosis warrant hospital admission.

The late fall in insulin needs must be anticipated and dosage cut without hesitation where falling blood sugar values dictate. Where Caesarean section or induction is planned, long acting types are better avoided on the chosen day, such insulin as is required being given in soluble form after completion of the operation.

Early recognition is one means of protection against severe toxæmia, and each case should be assessed early on, age at onset, duration of diabetes mellitus, vascular status and previous obstetrical history being taken into account in estimating its likelihood. White has done much to facilitate this and has devised six categories, starting with latent cases diagnosed only on an abnormal glucose tolerance curve, proceeding through grades determined by dates of onset and duration of diabetes, and ending up with cases of frank hypertension, calcification of pelvic arteries and renal involvement. The trend towards maternal morbidity and foetal mortality increases steadily throughout these grades and the strictest control therefore is exerted over patients in the later grades. Low salt diet and banning of sodium containing drugs such as bicarbonate is applied where oedema, hydramnios or hypertension manifest even in small degree. Some go further and use these restrictions in every case, either from the fifth month or even throughout the pregnancy. Where any substantial fluid retention develops ammonium chloride in doses up to four grams daily can be tried in addition to complete bed rest. Mercurial diuretics can be used to bring about further fluid loss if need be.

The use of *hormones* and whether to use oestro-

CLASSIFICATION OF OBSTETRICAL CASES AND BASIC PLAN OF DAILY HORMONAL TREATMENT (After White of Boston)

Classes	A	B	C	D	E	F
Definition	Glucose tolerance test.	Duration under 10. Onset over 20. Vascular o.	Duration 10 to 19. Onset 10 to 19. Vascular o.	Duration over 20. Onset less than 10 years. Vascular. Calc. in legs, retinitis.	Calcified pelvic arteries.	Nephritis
Per cent. of series ..	4	28	37	22	7	2
Hormone dosage of stilboestrol and proluton in milligrams of each, preferably by i.m. route						
Week of Pregnancy.		I.M.	I.M.	I.M.	I.M.	I.M.
0-10	0	5	5	10	25	25
16-20	0	5	5	10	25	25
20-24	0	10	10	15	50	50
24-28	0	15	25	25	75	75
28-32	0	25	25	50	100	100
32-onwards ..	0	50	50	75	125	125
Probable Delivery Week	40	38	38	35	35	Viability.

Therapy regulation based upon:

1. Weekly serum chorionic gonadotropin and urinary pregnandiol (glucuronidate) levels.
2. Clinical evidence of disturbed water balance.

gen alone or together with progesterone is optional. Each must decide for himself after consideration of the conflicting views. It must be reaffirmed that careful supervision and control being equal, the use of these has effected no greater improvement in either maternal or foetal abnormality in many clinics of high repute, including that of Lawrence. As the theory, however, has been shown to be virtually free from deleterious side effects either during or after the pregnancy, it may be justifiable to use them in the long standing case with definite vascular change carrying an admittedly poorer prognosis as well as where a previously bad obstetrical history is obtained. Details of dosage of stilboestrol and progesterone are given in the accompanying table which includes White's methods of classification and her preference for date of delivery. Where stilboestrol is used alone the dose is graduated throughout to amount to 160 mgm. daily in the final month.

Interruption of pregnancy before term is perhaps the most profitable precautionary measure, applying to all except the mildest cases and those few with a satisfactory obstetrical history. The choice lies between Caesarean section and surgical induction.

With the recognition of the special risks to the baby in the last four to six weeks of pregnancy it was, and still is in this country, common practice to carry out planned Caesarean section at 35-38 weeks, usually at 36 weeks. Thereby excessive prematurity and intra-uterine foetal deaths are largely avoided. Two thirds of cases in many centres are still handled in this way, the appro-

priate date being determined by consideration of all aspects. Thus, long established disease, early age of onset and evidence of vascular disease in the mother, dictates the earlier date which is also indicated when there is a story of previous obstetrical accidents or where uncontrollable toxæmia or diabetic ketosis exist.

Induction is followed not only by an unpredictable delay in the onset of labour but labour itself is likely to be prolonged and difficult. The babies concerned stand lengthy labour extraordinarily badly and maternal diabetes is likely to present a serious problem in control as both vomiting and obstinate anorexia may supervene. It is not difficult to see why this method is often discarded. There is, however, an increasing reaction in favour of this procedure in the United States. Where premature delivery is decided upon the pelvic route is preferred, artificial rupture of the membranes being carried out provided always that the state of the cervix is favourable. Caesarean section is then reserved for accepted obstetrical indications; postmaturity and strong evidence of the presence of a giant foetus; abnormal presentation; or older primiparae and multiparae with a poor past history. These conditions cover a substantial number of cases.

Providing a good colour is maintained and cyanosis avoided, the choice of anaesthetic is open, though deep general anaesthesia is patently contraindicated. The spinal route is often advocated but gas and oxygen with small amounts of cyclopropane or trilene are used as often and as satisfactorily. In the interests of the foetus, no sedative

such as morphine or a barbiturate is ever allowed, atropine being the sole premedication.

Arguments against the use of any form of premature delivery are gaining strength and are based on the increased risk to life that prematurity forces on a child already holding reduced chances of survival. Recently, attempts are being made to allow cases to proceed without interference and to terminate in natural births. Barns and Morgans adopting this policy estimate that any added foetal loss by death in utero can be set against an improved neonatal survival rate. A much more extensive group of cases must be watched before their conclusions are justified and before the accepted method of early Caesarean section carrying certain improvement in foetal survival rates should be abandoned.

To come to the right decisions as to whether to terminate, the best time to choose, the right method to use, each case should be completely reviewed at 35 weeks, preferably in hospital.

It is abundantly clear from what has already been said that exceptional care must be afforded the infant, irrespective of the manner of its birth. Gentle handling, especially of the fragile head, during delivery and after, warmth and a clear air way are the fundamentals. Upper air passages must be cleared with a mucus catheter and gastric suction employed to avert inhalation of stomach

contents. Incubation with oxygen is needed for three to five days, according to the maturity and response of the infant. No fluid is given in the first forty-eight hours during which oedema subsides and considerable weight loss results from spontaneous diuresis. Hypoglycaemia not being considered to contribute much to neonatal problems, glucose should not be given. If the infant does well to the third day it stands a good chance of survival. Later deaths are accounted for by congenital defects or by birth injuries.

In conclusion it must be emphasized that not all diabetic women are subject to these hazards. A small number escape and undergo a normal pregnancy, terminating naturally in the delivery of a healthy full-term child. One such experience is a good portent for continued uneventful child-bearing. Unfortunately, no simple means has yet been devised to distinguish this fortunate group from the unfortunate majority who will be exposed to the more eventful course. Even were hormonal imbalance accepted as the critical factor in the evolution of abnormality, the estimations required for its detection are time consuming, difficult and expensive and could not be applied on any wide scale. It is better to regard all diabetic pregnancies as potentially abnormal unless assurance from a previously excellent obstetrical history is available.

CARCINOMA OF THE HEAD OF THE PANCREAS

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Cancer of the pancreas has not long been considered a possible, let alone a profitable, field for excisional surgery. Until about twenty years ago very few attempts had been made to perform more than a palliative operation, though a certain number of local, conservative resections had also been carried out and one radical pancreato-duodenectomy similar to the modern operation had been attempted, though without success, by Codivilla as early as 1898.

The middle 1930s saw a considerable revival of interest in this difficult branch of surgery, and the advent of vitamin K in 1935, which so greatly reduced the risk of operating upon a jaundiced patient, naturally had a good deal to do with the progress made. In this year (1935) Whipple and his associates described their two-stage procedure for the radical resection of a carcinoma of the

ampullary region and a great deal of the credit for reviving interest in pancreatectomy for cancer must be given to these authors. In 1937 Brunschwig successfully removed a carcinoma of the head of the pancreas using a similar two-stage procedure.

These islands and the Commonwealth did not lack surgeons of skill and high courage interested in the surgery of this region. Gordon-Taylor, James Walton and Illingworth are names that at once spring to mind, while Victor Hurley of Melbourne had a success with resection by the retro-duodenal route. No one who heard Gordon-Taylor about this time will forget his enthusiastic insistence that radical surgery must be attempted on all suitable cases. His papers in 1942 and 1943 referred to several successful cases of his own, though his technique in those days was less