

Pregnancy and diabetes

(A Review of some results and problems at the Kandang Kerbau Hospital)

by

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There are many aspects of glamour in Obstetrics at large, but one of the foremost aspect is the fact that there is an incidence of very intimate inter-relations in Obstetric problems between the Obstetricians, Physicians and Paediatricians. This is very true especially in the problem of Pregnancy and Diabetes. In the State of Singapore today, with an island wide population of approximately 1.7 million, there are 2 concerted diabetic clinics run and organised by two established medical Units and I am told this will be joined in due course by a third clinic to be run by the third medical unit. Regrettably, however, there has been no published reports about the extent of this medical problem and neither has there been any report of the incidence of Diabetes and Pregnancy as occurring in the State. I would like to think that the time is now ripe, if not already too ripe, to have a Central Agency—an island wide organisation to be responsible for a unified registration and control of all diabetics in the State. This organisation can be called by any name—The Singapore Association for Diabetic Control or call it what you may.

There are many reports in the literature from other countries about the problem of Pregnancy and Diabetes. Some series are small being personal experiences and some large series are in effect, a summation of the smaller series and, therefore, comparisons between such small series are naturally difficult and are of only limited value. For my part, it will be difficult in the cramped hour of one small afternoon to deal with all aspects of such a varied problem and I propose only to deal with 3 aspects of the problems as encountered in practice at the Kandang Kerbau Hospital in recent years. The period covers the years 1960

to 1963 and the aspects of the problems covered include:—

1. Incidence
2. Maternal Mortality
3. Perinatal Mortality

Incidence:

A review of most of the available literature on the incidence of diabetic pregnancies show such a wide variation that one begins to doubt the accuracy of any such reported incidence. Thus, for example, in Table I—at the Queen Charlotte's Hospital, there had been 14 diagnosed cases of Diabetic Pregnancies in 40,000 deliveries—an incidence of 1 case in approximately 2,857 deliveries. The King's College Hospital (Peel) reports an incidence of 1 in 50 pregnancies and a study of other centres shows an average incidence of 1 in 300 preg-

TABLE I

Diabetic Pregnancies—Incidence

Queen's Charlotte	14 in	40000
	1 in	2857
King's College (PEEL)	1 in	50
Average from 12 centres	1 in	300
Kandang Kerbau	90 in	150164
(1960—63)	1 in	1662
Heart Disease	0.2 to 1.0 per cent	
Tuberculosis	0.7 to 1.5 per cent	

nancies. At the Kandang Kerbau Hospital, analysis over a 4 year period 1960 to 1963 show a total of 90 cases in 150164 pregnancies (deliveries) or 1 in 1662 pregnancies (deliveries). There are difficulties encountered in working out the incidence and these include the interpretations of the Glucose Tolerance Curves. Different countries and different centres adopt different standards in the assessment and diagnosis of a diabetic tolerance curve and even in the same country, different authorities might adopt different interpretations. I think a plea should now be made that in an insular State like Singapore, where most authorities have easy access and know one another well, a set standard should be adopted for the whole State. The criteria adopted by the Mayo Clinic, Rochester U.S.A. as shown in Table II appears

TABLE II
Glucose Tolerance Test
MAYO CLINIC STANDARD

	Blood Glucose mg. per 100 ml.		
	Normal	Equivocal	Abnormal
Fasting	65 to 90	91 to 110	Over 110
1 hour	140 or less	141 to 150	Over 150
1 hour	90 or less	91 to 100	Over 110

to be a sensible standard for adoption. (Proc. Staff Meeting—Mayo Clinic 1963, Vol. 38 No. 6). These difficulties do not appear to exist in Pregnancies with Tuberculosis and Heart Diseases and for comparative reasons, the respective incidence are appended as follows:—

Tuberculosis - 0.7 to 1.5 per cent
 Heart Disease - 0.2 to 1.0 per cent

Studies on the incidence and subsequent diagnosis of Diabetes in pregnant patients at the Kandang Kerbau Hospital disclose some interesting data which are presented in the hope that we may recognise our pitfalls and set about a proper anterospective scheme of study of these cases. Table III shown clearly an increasing awareness of the necessity of carrying out Glucose Tolerance Tests on cases which show Glycosuria in pregnancy. Thus in 1960—only 13 recorded cases of G.T.T. were done in the Hospital for which four confirmed cases of Diabetes were found. In 1963, a total of 213 cases of G.T.T. were carried out in this Institution giving a 17 times increase and of these, 41 cases of confirmed Diabetics were diagnosed. This is indeed one of the healthy signs for this Institution and what is required will be the necessity of every case of Glycosuria being subjected to G.T.T. studies and every case tagged until delivery and throughout their reproductive life. As stated earlier, it will be necessary to accept one standard such as the Mayo Clinic standard in order to make a diagnosis of Diabetes. It is also interesting to note that the number of deliveries in 1960 at 36,267 is near identical to the 1963 figure of 39,436 deliveries.

TABLE III

Year	No. Deliveries	G.T.T. Done	No. Confirmed
1960	36,267	13	4 (30.7%)
1961	36,590	34	21 (61.7%)
1962	27,861	87	24 (27.6%)
1963	39,436	213	41 (19.2%)

TABLE IV

1960-63	Races	No. Deliveries	No. Cases	Incidence
	Chinese	157,392	55	1 in 2860 deliveries
	Malaysians	40,884	17	1 in 2405 ..
	Indians	17,742	16	1 in 1109 ..

Racial Incidence:

The distribution of the Diabetic Pregnancies amongst the various racial groups at the Kandang Kerbau Hospital also provide some interesting facts as in Table IV,

There would appear to be little difference in incidence between the Chinese patients and the Malaysians (Malays and Indonesians) but the incidence amongst the Indian patients presents a figure of statistical significance. I think it is quite true to say that person for person, the incidence of Diabetes Mellitus at large amongst the Indian population is higher than the other racial counterparts and this applies equally true to pregnant patients.

Age and Parity Incidence:

The Age and Parity incidence amongst the diagnosed pregnant Diabetics at the Kandang Kerbau Hospital are shown in Table V and VI:—

The Table tends to show that there is two-fold increase in the chances of picking out a diabetic in a pregnant patient over the age of 30 years than in those under 30 years of age. Only two cases in this series may be truly said to be cases of juvenile diabetes and it is reasonable to assume that age, succeeding years and perhaps succeeding pregnancies are associated factors which tend to unmask diabetes in a pregnant patient.

TABLE V—Age Incidence (1960-63)

Years	16-20	21-25	26-30	31-35	36-40	41-45	Over 45
	2	7	18	29	21	13	Nil
Over 30 years	-	-	63 cases	-	-	-	70.0%
Under 30 ..	-	-	27 ..	-	-	-	30.0%

TABLE VI—Parity Incidence (1960-63)

	1	2	3	4	5	6	7	8	9	10	11	12/Over
	8	9	8	5	9	8	8	10	8	6	4	7
Para. 1	-	-	-	-	8 cases	-	-	-	-	-	-	0.88%
2 to 5	-	-	-	-	31 ..	-	-	-	-	-	-	34.40%
6 and Over	-	-	-	-	51 ..	-	-	-	-	-	-	64.72%

The figures on Table V attest to an oft-stated point that succeeding pregnancies ultimately unmask latent or pre-diabetes.

Another point of interest which has impor-

tance to both maternal and perinatal mortality figures in general is the question of the time of diagnosis and the time of institution of anti-diabetic treatment. This information is supplied in Table VII:—

TABLE VII—Time of Diagnosis and Time of Treatment

Weeks	18	20	22	24	26	28	30	32	34	36	38	40	A.D.	Total
Diagnosis	—	1	—	—	—	—	1	2	6	14	8	2	56	90
Treatment	—	1	—	—	—	—	1	2	6	14	8	2	—	34

9 cases treated before 219th Day - - - 10.0 per cent

56 „ Not treated at all - - - 80.0 per cent

Notice the large percentage 62% (56 cases) where the diagnosis was only made after delivery and only after suspicion has been cast because of large and over-weight babies or because of some tragic obstetric occurrence as a sequel of large babies with Shoulder Dystocia. Only 10 cases had been diagnosed at or before the 34th week and the remaining 24 cases were diagnosed at and after the 36th week—a period which to all purposes is crucial from the point of foetal salvage. These figures will be discussed again at a later point when

foetal macrosomia and perinatal mortality are discussed.

Maternal Mortality:

The discovery of Insulin and the resultant great improvement in the treatment of Diabetes Mellitus in general has not only brought increased fertility amongst Female diabetic patients but indeed it has been responsible for the great fall in maternal mortality from the high figure given by Whitridge Williams in 1909 of 45-50 per cent to the recent reported figures:—

TABLE VIII

Year	Author	Rate
1909	Whitridge Williams	45 to 50 per cent
1946	Oakley and Peel	2.2 per cent
1947	White	0.2 per cent
1948	Joslin	0.4 per cent
1956	Clayton	0.5 per cent
1958	Black and Miller	0.6 per cent
1959	White	0.3 per cent
1961	Hagbard	0.7 per cent
1963	Kandang Kerbau (90)	0.0 per cent

Toxaemia of Pregnancy

Oakley and Peel	-	10.7 to 18.9 per cent
Kandang Kerbau	-	23.3 per cent (21 cases in 90)

The cause of deaths have been attributed to poor control of maternal diabetes and associated morbidity associated with difficult and operative methods of delivery.

At the Kandang Kerbau Hospital over the years 1960 to 1963—a total of 90 diabetic mothers had been delivered and there had been no loss of even a single maternal life. This figure must not in any way be accepted to reflect that we have exercised an excellent mode of management of these pregnant diabetics—indeed far from it, for 68 patients (about 75%) in the series had received no treatment for the diabetes at all and had in one way or another, survived the hazards which are normally expected of an untreated pregnant diabetic. Besides it must be accepted that the series of 90 patients is indeed a small series to draw any concrete conclusions; for it may so happen that in the next succeeding 30 cases analysed, 2, 3 or 4 maternal deaths might be encountered. All that can be said at this time for this zero mater-

nal mortality rate is that this is an extremely lucky chance figure—a figure we might do well to produce all the time in the future.

Whilst at this point of mortality, it might not be too out of place to cite one special feature of morbidity which authorities have chosen to draw attention to when discussing pregnancy and diabetes. This concerns the problem of Toxaemia of Pregnancy. This is perhaps the most important maternal complication of Pregnancy in a Diabetic. Using the well known criteria adopted as regards Hypertension, Oedema and Albuminuria (Proteinuria)—Oakley and Peel in a review of reports from some centres have placed the incidence as varying from 10.7 to 18.9 per cent. At the Kandang Kerbau Hospital, amongst the 90 cases of Pregnant Diabetics—there were 21 cases with Toxaemia of Pregnancy, giving an incidence of 23.3 per cent. There will be considerable variations in the incidences when we consider that the major occurrence of this complication occurs in the last four weeks of Pregnancy and in the present accepted obstetric treatment of Diabetic Pregnancies, delivery is achieved some 2 to 4 weeks from term. Toxaemia of Pregnancy naturally carries also a high toll of perinatal deaths and this adds doubly to the impor-

TABLE IX—Foetal Mortality

Pre 1941	Oakley and Peel	-	-	-	-	-	-	-	32.6 per cent
	Gellis and Hsia	-	-	-	-	-	-	-	40.0 per cent
1947	White	-	-	-	-	-	-	-	10.0 per cent
1948	Oakley and Peel	-	-	-	-	-	-	-	25.4 per cent
1951-60	Hagbard	-	-	-	-	-	-	-	17.0 per cent
1950-56	Gellis and Hsia	-	-	-	-	-	-	-	17.0 per cent
1951-54	Adams	-	-	-	-	-	-	-	8.0 per cent
1950-57	Malins	-	-	-	-	-	-	-	17.0 per cent
1960-63	Kandang Kerbau (perinatal loss)	-	-	-	-	-	-	-	16.8 per cent
1961	Oakley and Peel	-	-	-	-	-	-	-	13.4 per cent

tance of this condition. Further, Toxaemia of Pregnancy leaves their mark in some 20 per cent of pregnancies in the form of residual hypertension or recurrent toxaemias in succeeding pregnancies.

Perinatal Mortality:

It has been stated that despite the discovery of Insulin and the recent endocrinological advances in the field of diabetes, the foetal mortality in Diabetic Pregnancies has not kept pace with the great decline of maternal mortality rates. The term Foetal Mortality in effect covers all cases of still-birth and deaths within the first month of neo-natal life. In this series under review at the Kandang Kerbau Hospital, perinatal mortality rate has been considered and the comparative and improvement figures over the years are shown in Table IX.

1. Intra-Uterine Foetal Hypoxia

- a) Uterine Blood Flow—Brudennel
- b) Oxygen content, saturation and capacity in Cord Blood.
- c) Haemoglobin Level in Cord Blood.

2. Hormone Deficiency

Pregnanediol Studies - White
Smith/Smith
Peel
Edinburgh

Estriol Excretion - Zondek et al
10 mgm/24 hours Greene et al
Under 4 mgm./24 hours

In the neglected and untreated diabetic women, it is generally accepted that a high percentage will end in intra-uterine death of the foetus and this tends to occur predominantly in the last trimester of Pregnancy. The same sequence of events will still occur in the pre-diabetic patient and similarly in those who

have been adequately controlled to the point of absent hyperglycemia and ketosis. In the series under review at the Kandang Kerbau Hospital, there had been a total of 13 perinatal deaths in 90 diabetic pregnancies—a rate of 16.8 per cent. 6 out of these 13 perinatal deaths were in effect intra-uterine deaths—a rate of 6.6 per cent. As intra-uterine deaths predominantly occur in the last 4 weeks, one aspect of obstetric management in order to prevent this occurring, would be to terminate the pregnancies prior to this event. Too early intervention however, would achieve delivery of a live baby only to face the hazards of immediate neo-natal life to which an immature infant will face and might easily succumb. The incidence of respiratory difficulties in such cases especially pulmonary hyaline membrane disease is high in such instances. It would thus appear that if we are able to have some idea and some warning signs of when an intra-uterine catastrophe will occur, we might then be able to decide the nearest possible date to term in order to deliver a mature infant with a higher resistance to immediate neo-natal hazards. There have been some aspects of work which have been done in special clinics in Britain and America and I would like to discuss some of these and to draw some relevance to this series at Kandang Kerbau Hospital where ever possible.

(a) Intra-Uterine Foetal Hypoxia

It has been reasonably suspected by White and Hunt that advancing age in an individual might cause calcification changes in the uterine arteries and this will give rise to placental ischaemia. Thus studies related to foetal hypoxia have been carried out in attempt to see if foetal hypoxia as such does really cause intra-uterine deaths in Diabetic Pregnancies. Three aspects of work related to this view of thought have been done as follows:—

1. Morris et al—using radio-active Na 23 has made attempts to demonstrate uterine and placental blood flow capa-

cities in cases of Toxaemia, hypertension, hydramnios and multiple pregnancy. Work at the King's College Hospital by Bruoenel under Peel show that there was no appreciable difference in uterine blood flow between diabetic pregnancies and pregnancies with Toxaemia, Hydramnios and multiple pregnancies. However, the same worker had shown that there IS an appreciable difference between the clearance times in cases where the baby survives in a diabetic pregnancy and in the group of cases where there was intra-uterine death. But the significant difference was in an opposite direction from what has been generally anticipated in the sense that blood flow was faster in those cases where intra-uterine death had occurred as compared to those cases where the foetus had survived. At the same time, it was also convincingly shown that with Insulin therapy, uterine blood flow in most cases was faster than in those cases with no insulin therapy. It is felt that these are strange findings and, therefore, difficult to draw any significance.

2. Oxygen content, saturation and capacity in Cord Blood studies have been done by Walker, Mackay and Clemetson et Churchman with a view to correlate foetal hypoxia in toxæmic, hypertensive and past date pregnancies. These procedures of course have recognised technical difficulties. Work on these lines on diabetic pregnancies have again been carried out at the King's College Hospital but the number of cases have been few and here again, no significant conclusions can be drawn. Similarly studies of Haemoglobin Level in the Cord Blood have been carried out and there is no evidence found to show that hypoxia as such occurs in Diabetic Pregnancies.

At this institution in Singapore, no facilities for such aspects of work are available and I am afraid that we will have to admit that we will not be able to enter this field of study

until such laboratory facilities are made available.

(b) **Hormone Deficiency**

Chiefly through the work of White et al and Smith and Smith, the concept of a possible hormone deficiency in Diabetic Pregnancies which could account for intra-uterine death of foetuses was strongly held for some time. It had gathered more ground by the improved results in foetal mortality in which White and Nelson et al have been able to achieve using the regime of treatment as set out by Smith and Smith for cases of threatened abortion. This work involving hormone assays and pregnanediol excretion assays were conducted at the Edinburgh School and by Peel at the King's College Hospital. The substance of reports from these two centres form the conclusions of a Medical Research Council report that no progesterone deficiency could be amply demonstrated in diabetic women to allow inference that hormone deficiency and placental deficiency go hand in hand in the production of intra-uterine death in such pregnancies. Perhaps more help may be forthcoming in this direction with advances in techniques for assaying blood progesterone levels and Estriol levels to help us reach some conclusions in this light and thereby prognosticate the outcome of diabetic pregnancies.

Again, in this respect, no work on these lines had been possible at the Kandang Kerbau Hospital and, therefore, no comments can be made on our cases.

(c) **Foetal Macrosomia**

From a practical point of view, diabetic pregnancies are characterised by over-sized and over-weight babies which nevertheless die either through difficulties with dystocia especially shoulder dystocia or some other factors associated with poor tolerance of immediate neo-natal hazards.

The exact cause of foetal macrosomia is not definitely understood since macrosomia must be dependent on both parental genetic factors and also with the age and parity of the mother. It is accepted that birth weight increases with maternal age and decreases with increasing parity and also it has been definitely

shown that birth weights are higher in foetuses born of diabetic fathers but healthy mothers (Kellock). It has also been amply shown by Hagbard, Hsia et Gellis in the U.S.A. and Cardell at the King's College Hospital that birth weights of babies of diabetic mothers are significantly higher than those of non-diabetic mothers. But these significant differences were only appreciable if the cases were treated after the 219th day of pregnancy or where no treat-

ment had been carried out at all. In cases where treatment for the diabetes had been commenced prior to the 219th day of pregnancy, so such appreciable difference in birth weights was reported. The same conclusions were drawn if hormones were used in treatment of these cases with the diabetic pregnancies. The Table below shows such observations as reported by the various authors:—

TABLE X

	Average Birth Weight	
	Treated	Not Treated
(a) Lawrence and Oakley	6lbs. 15 ozs.	10 lbs. 2 ozs.
(b) Pedersen	Comparable difference of 190 grams.	
(c) K.K. Hospital	7 lbs. 4 ozs.	8 lbs. 8 ozs.

One recent aspect of work which has some significance in the study of foetal macrosomia is the possible fact that reduction in the birth-weight of infants born of treated diabetic mothers is in fact an overall reduction in the weight of the various organs and not as was once supposed a dissolution as it were of subcutaneous fat and tissue oedema. Recent work by Ehrlich and Randle has shown that Foetal macrosomia in untreated diabetic pregnancy is associated with a higher concentration of Serum Human Growth Hormone (HGH). The normal varies from 10 to 30 ug but in one case of foetal macrosomia, the HGH reached a figure of 72 ug.

Whilst on the subject of Foetal Macrosomia, it will not be out of place to say some words about the phenomenon of Pre-Diabetes which condition appears to be in some state of uncertainty and confusion. Pre-Diabetes properly refers to that period which ante-dates the appearance of an abnormal standard GTT. Pre-Diabetes and unrecognised diabetes should not be confused for they are not synonymous. The term "latent diabetes" tends to add more to the confusion but this term is strictly reserved for that period of apparently normal carbohydrate metabolism following a period of distinctly abnormal carbohydrate tolerance. In other words, latent diabetes implies a period

during which previously demonstrable diabetes cannot be demonstrated by the standard diagnostic procedures but with stress tests, diabetes can be demonstrated. Peel has suggested that there are 4 occasions when one can call a case Pre-Diabetes:—

1. Pregnancy ending with a foetal macrosomia, unexplained intra-uterine death or unexplained peri-natal death. Glucose Tolerance Tests may be normal but if the case is followed sufficiently for a number of years, frank clinical diabetes will develop.
2. A familial history of Diabetes and with Pregnancy Obesity. Glucose Tolerance Tests are normal.
3. Suspicious Glucose Tolerance Tests with Steroids. Renal Glycosuria is present but Glucose Tolerance Test is normal without steroids and fasting blood sugar levels are normal.
4. Pregnancy Glycosuria and Frank Diabetes during a Pregnancy but no symptoms are the end of a Pregnancy.

Using this criteria to describe the condition of Pre-Diabetes, there had been 14 cases as such

in the 4 year period under review—an incidence of 15.5 per cent.

(d) Foetal Mortality and Obstetric Management

It has already been stated that in diabetic pregnancies left untreated, untra-uterine death will occur especially during the last four weeks. Foetal mortality is, however, also dependent on the presence of other complications such as Toxaemia, Hydramnios and congenital malformations. Complicated diabetic pregnancies will, therefore, incur a much higher foetal mortality rate.

Peel has indicated that in his experience with 584 diabetic pregnancies spread over many years, his best results had been obtained with the group of patients whom he had admitted from the 31st week of pregnancy and kept until delivery. In these patients there is ensured adequate control of the diabetes and proper prevention of Toxaemia and its complications.

There is an increasing tendency to terminate all diabetic pregnancies at or around the 37th week. Whether labour is to be achieved by vaginal delivery following induction or by

Caesarean Sections must vary from case to case. On the whole, it is concluded that better results are obtained with deliveries by Caesarean Sections than by vaginal deliveries but analysis will tell you that on detailed studies, significant evaluation is difficult. Nevertheless it must be clear that Caesarean Section is only one factor involved in foetal salvage for there must be other factors at play.

Some of the comparative published results are appended in Table XI and at the Kandang Kerbau Hospital, the position appears to be the reverse of other published reports. The perinatal mortality rate showed 25.0 per cent for deliveries by Caesarean Sections and only 12.8 per cent for vaginal deliveries. Further studies of these cases however showed that the cases delivered by Caesarean Sections were severe cases of diabetes, complicated in instances by Toxaemia and hydramnios and foetal distress. The deaths incurred by Caesarean Sections were not still-births but were deaths occurring the first week of life.

The break-down details of the mode of deliveries of the 90 Diabetic Pregnancies at the Kandang Kerbau Hospital are as in Table XI:—

TABLE XI—Factors In Foetal Mortality Mode of Termination of Pregnancy

	LSCS	Vaginal
Gellis and Hsia (1959)	10.7 %	13.7%
Dolger et al (1960)	12.0%	14.8%
Shlevin (1958)	7.0%	4.3%
Kandang Kerbau	25.0%	12.8%

Break-Down of Deliveries—Kandang Kerbau 1960-63

Delivery	Alive	SB	ND	Total
LSCS (Elective)	9	—	3	12
VAGINAL				
Spontaneous	32	2	1	35
Induced	37	4	3	43

Induced Group—Mode of Delivery

Spontaneous	15	2	—	17
With Pitocin	1	—	—	1
Forceps	2	2	—	4
LSCS	18	—	3	21

In conclusion, it can be stated that there is much room now for more intensive studies of our Pregnant Diabetics. I am inclined to feel that a centralised and concerted programme for study of such patients should be evolved. There should be a more acute look-out for cases of Pre-Diabetes and that much liaison should be established between the Hospital and the Maternal and Child-Health as well as the General Practitioner Clinics so that all cases could be referred to one centre for unified attention. Last but not least, the evolved Unit should include a specialist Physician with a special interest in Diabetes, an Obstetrician and, of course, a Paediatrician.

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