# RETROSPECTIVE ANALYSIS OF PREGNANCIES AT THE GROOTTE SCHUUR HOSPITAL.

## A COMPARISON OF PREGNANCY OUTCOMES IN PRE-GESTATIONAL AND GESTATIONAL DIABETES



BY

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# DEDICATION

This work is dedicated to my parents; late Chief G.O.M Ekpebegh and Mrs M.I Ekpebegh for their selfless sacrifices to educate me and to my dear wife Dr Doreen C Ekpebegh for her support throughout the duration of the study; but above all this thesis is dedicated to the glory of God Almighty for his grace and mercies.

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## ABBREVIATIONS

ACHOIS: Australia Carbohydrate Intolerance Study

ACOG: American College of Gynecology

ADA: American Diabetes Association

AFI: Amniotic Fluid Insulin

BMI: Body Mass Index

CI: Confidence Interval

CVS: Cardiovascular system

CPD: Cephalo-Pelvic Disproportion

DCCT: Diabetes Control and Complications Trial

DFPG: Diagnostic Fasting Plasma Glucose

DM: Diabetes Mellitus

EASD: European Association for the Study of Diabetes

FPG: Fasting Plasma Glucose

GA: Gestational Age

GCT: Glucose Challenge Test

GDM: Gestational Diabetes Mellitus

GIGT: Gestational Impaired Glucose Intolerance

Gli: Glibenclamide

Glicz: Gliclazide

GSH: Grootte Schuur Hospital

HAPO: Hyperglycaemia and Adverse Pregnancy Outcome

HbA1c: Glycated Haemoglobin

HPLC: High Performance Liquid Chromatography

IAPP: Insulin Amyloid Polypeptide

IDF: International Diabetes Federation

Kcals: Kilocalories

MBG: Mean Blood Glucose

Met: Metformin

mmol/l: millimoles per litre

NA: Not Available

NDDG: National Diabetes Data Group

NND: Neonatal Death

NPH: Neutral Protamine Hagedorn

OGLA: Oral Glucose Lowering Agents

OGTT: Oral Glucose Tolerance Test

OR: Odd Ratio

PCOS: Polycystic Ovarian Syndrome

PNM: Perinatal Mortality

PNMS: Peninsula Maternal and Neonatal Service

PPG: Post-prandial Glucose

PPW: Per Pregnancy Weight

RCCT: Randomized Controlled Clinical Trial

SB: Stillbirth

S.E.M: Standard Error of Mean

SMBG: Self Monitoring of Blood Glucose

USPTF: United States Preventive Task Force

Vs: versus

WHO: World Health Organization

## SUMMARY

**BACKGROUND AND OBJECTIVES:** In developing countries insulin, which is the internationally accepted standard for glycaemic control in pregnancy, is not universally available. Consequently, there is the need to assess the safety of oral glucose lowering agents (OGLAs) as an alternative to insulin for glycaemic control in pregnancy. Although the treatment of gestational impaired glucose tolerance (GIGT) has been shown to be beneficial, the cost implications in treating GIGT in resource constrained economies needs examination. Thus this study assessed: (i) pregnancy outcomes in pre-gestational types 1 and 2 diabetes (DM) with particular emphasis on the modality of therapy for pregnant women with type 2 DM, (ii) pregnancy outcomes in subjects with gestational diabetes (GDM) and the effect of stratification by fasting plasma glucose (FPG) and 2 hour oral glucose tolerance test (OGTT) plasma glucose values, and (iii) the effect of OGLAs on pregnancy outcomes in GDM.

**METHODS:** We conducted a retrospective analysis of the maternal and perinatal outcomes of pregnant subjects with types 1 and 2 DM who delivered at Grootte Schuur Hospital (GSH), a tertiary health care facility in Cape Town from 1991 to 2000. A similar analysis was done on GDM subjects who delivered at GSH from 1995 to 1997.

The type 2 DM subjects were categorized into 3 treatment groups based on treatment in pregnancy: OGLAs alone, converted from OGLAs to insulin and diet/insulin alone.

The GDM subjects were categorized as DM or IGT based on diagnostic FPG and the 75gram OGTT 2hour plasma glucose levels. The GDM subjects were further subdivided based on treatment in pregnancy into 4 treatment groups: diet alone, OGLAs alone, converted from OGLAs to insulin and insulin alone.

The case records of eligible subjects were reviewed after ethical approval was obtained from the institutional ethics committee. Demographic data, measures of glycaemic control, mode of therapy, maternal and perinatal outcome variables were abstracted.

**RESULTS:** One thousand, one hundred and twenty five (1125) pregnancies were studied (578 pre-gestational and 547 gestational DM).

The PNM rate (per 1000) was higher in treated type 1 compared with treated type 2 DM subjects, 67.1 vs 35.9, $p<0.05$. The rates of PNM, fetal anomaly and neonatal jaundice were higher in untreated compared with treated type 1 DM patients. The rates of PNM, fetal anomaly and pre-eclampsia were higher in untreated compared with treated type 2 DM patients. The PNM rates (per 1000) corrected for untreated patients were: 67.1 in type 1 diabetes, 93.8 in OGLAs

alone treated type 2 DM, 24.8 in the type 2 DM group converted from OGLAs to insulin and zero in the diet/insulin alone treated type 2 DM group ($p < 0.05$). Correction of PNM rate (per 1000) for fetal anomalies associated with PNM resulted in an additional decline in PNM rates (per 1000) to 15.5 in type 1 diabetes, 16.7 in type 2 DM group converted from OGLAs to insulin while that of OGLAs alone treated type 2 DM, remained unchanged at 93.8 ($p < 0.05$). Chi square analysis demonstrated significant difference in the uncorrected PNM rates between the various groups with higher observed than expected rates in type 1 DM and OGLAs alone treated type 2 DM group.

In pre-gestational type 2 DM subjects the presence of fetal anomalies (Odds ratio (OR); 34.6; 95% confidence interval (CI) 2.7-444.5; p=0.006), treatment with OGLAs throughout pregnancy (OR 5.2; 95% CI, 1.4-18.8; p=0.01) and the last HbA1c before delivery; (OR 1.7; 95% CI, 1.1-2.6; p=0.01) were all independently associated with PNM in multivariate logistic regression analysis. The presence of fetal anomalies was however, no longer a significant predictor of PNM when untreated patients were excluded from the multivariate analysis.

The fetal anomaly rate for all the pregnancies exposed to oral agents in the 1$^{st}$ trimester (calculated by combining type 2 DM subjects who were only treated with OGLAs and those converted from OGLAs to insulin) was 3.1%. The rates corrected for untreated patients were 2.3% in type 1 DM, 1.6% in OGLAs alone treated type 2 DM subjects and 1.7% in type 2 DM subjects converted from OGLAs to insulin.

Pregnancy outcomes in treated GDM were similar regardless of whether it was DM or IGT. The rates of PNM and macrosomia were significantly higher in the untreated DM compared with treated DM subjects. The untreated and treated IGT subjects had similar pregnancy outcomes. The pregnancy outcomes of IGT subjects did not differ on stratification by diagnostic FPG levels ie: ≥5.5 and <5.5 mmol/l nor on stratification in relation to the 2hour OGTT plasma glucose levels ie, < 9.0 mm0l/l and ≥ 9.0 < 11.0-mmol/l. The 3$^{rd}$ trimester PPG; (OR 2.3, CI: 1.1-4.6, $p < 0.05$), FPG at diagnosis; (OR 1.4, CI: 1.1-1.8, $p < 0.05$) and 2-hour OGTT plasma glucose value; (OR 1.2, CI: 1.0-1.5, $p < 0.05$) were significant predictors of PNM in univariate analysis of GDM subjects. In multivariate analysis of all GDM subjects with 3$^{rd}$ trimester PPG, diagnostic FPG and 2hour OGTT plasma glucose as independent variables, only 3$^{rd}$ trimester PPG remained significantly predictive of PNM (OR 2.1, CI: 1.0-4.5; $p < 0.05$). While booking HbA1c was above target goals in types 1 and 2 DM they were normal in GDM subjects.

**CONCLUSIONS:** The last HbA1c before delivery was significantly predictive of PNM in pre-gestational type 2 DM while the 3$^{rd}$ trimester PPG level was predictive of PNM in the cohort of GDM subjects. The limitation in the use of HbA1c as a marker of glycaemic control particularly in GDM is shown by the fact that mean

HbA1c levels at booking and in the 3rd trimester were normal and comparable in the subsets of treated and untreated GDM subjects while glycaemic profile assessed by FPG and PPG levels often differed.

Although retrospective in nature, this study supports the notion that metformin and probably glibenclamide are not teratogenic. Whilst the use of OGLAs in GDM was not attended with increased PNM, OGLAs alone throughout gestation in pre-gestational type 2 DM was associated with increased risk of PNM. Treatment of newly diagnosed frank diabetes in pregnancy had clear benefits with PNM rates lower than that of untreated diabetes subjects, but treated and untreated GIGT subjects had similarly low PNM rates. Stratification of GIGT subjects by diagnostic FPG or 2hour OGTT plasma glucose value did not identify any group at greater risk of increased PNM.

To what extent GIGT should be treated in societies where there are competing demands on scarce resources remains unanswered.

# CHAPTER 1: INTRODUCTION

Diabetes in pregnancy may represent pre-gestational diabetes; i.e. diabetes mellitus (DM) existing before pregnancy (type 1, 2 and others) or gestational diabetes (GDM) (1,2). The significance of diabetes in pregnancy lies in the adverse fetal and maternal outcomes compared with pregnancies in glucose tolerant women.

Conventional therapy for diabetes in pregnancy is diet with or without insulin. The use of oral glucose lowering agents (OGLAs) on the other hand has not been popular for reasons such as poor efficacy, increased risk of neonatal hypoglycaemia and concerns of teratogenicity (3). Insulin, which is internationally regarded as the standard for glycaemic control during pregnancy in women with diabetes, is however, not readily available to all that need it in resource constrained economies such as those of sub-Saharan Africa.

Oral glucose lowering agents may be alternatives to insulin for the management of glycaemia in pre-gestational and gestational type 2 DM if shown to have comparable pregnancy outcomes as insulin. This will have a positive impact on the management of diabetes in pregnancy for communities where insulin is not readily available. Oral glucose lowering agents have the advantage of convenience relative to insulin since they are taken orally with prospects for enhanced compliance. They are also cheaper than insulin, which requires syringes and needles for injections and the need for proper patient education on the appropriate methods of storage and administration. Insulin also needs storage facilities such as a refrigerator, which may not be affordable by diabetic patients in resource constrained societies.

There are indications that OGLAs may not be teratogenic in gestational diabetes as diagnosis and treatment is usually after the critical period of teratogenesis. Indeed the current ADA recommendations on pre-conception care of women with diabetes (4) is silent on the use of OGLAs in late pregnancy and only states that the safety of OGLAs in early pregnancy cannot be assured. The International Diabetes Federation (5) currently suggests that the use of glibenclamide/metformin may be justifiable in communities with a high prevalence of type 2 DM and tenuous supply of insulin.

There has been a recent recommendation for universal screening and treatment for all with gestational impaired glucose tolerance (GIGT) (6). This followed the report of the Australian Carbohydrate Intolerance Study (ACHOIS) in pregnant women (7) which demonstrated the benefits of treating GIGT. The cost implications in treating all GIGT in resource constrained economies however, needs examination, given the rising prevalence of gestational diabetes (8) and the fact that universal rather than the cheaper option of selective screening for gestational diabetes will be required to detect all GIGT. This is likely to impose enormous burden on the very limited health budgets of poor countries. Perhaps

stratification of GIGT subjects by fasting plasma glucose (FPG) and 2 hour oral glucose tolerance test (OGTT) plasma glucose criteria may identify a subgroup that will most benefit from treatment given the meager finances of developing countries.

The aim of this study was to assess the maternal and perinatal outcomes in women with type 1, type 2 and gestational diabetes managed at Grootte schuur hospital obstetric unit.

Objectives:

1. To assess the maternal and perinatal outcomes in women with type 1 DM.

2. To assess the maternal and perinatal outcomes in women with type 2 DM and GDM based on treatment modality namely: oral glucose lowering agents (OGLAs) alone, converted from oral glucose lowering agents to insulin (OGLAs to insulin), diet/insulin groups.

3. To determine the impact on maternal and perinatal outcomes in the subset of GDM subjects with GIGT after stratifying by FPG and 2hour OGTT plasma glucose levels.

# CHAPTER 2: LITERATURE REVIEW

## 2.1 ADVERSE PREGNANCY OUTCOMES

The adverse outcome in diabetic pregnancies has been consistently linked to poor glycaemic control and less so to the therapeutic modalities employed in achieving glycaemic control. Untreated DM in pregnancy is associated with adverse maternal and fetal outcomes (9-13). Even mild hyperglycaemia has been shown to be a risk factor for fetal morbidity (13,14). The treatment of patients with an abnormal 50 gram, 1hour glucose challenge test but normal response to 100 gram, 3hour OGTT decreased the occurrence of macrosomia (13) while the treatment of IGT resulted in lower rates of macrosomia (14). Indeed, early institution of tight metabolic control can prevent the excess mortality and morbidity typically observed in GDM (15). Although the institution of normoglycaemia throughout gestation may normalize morbidity and mortality for both infant and mother (16), caution needs to be exercised as aggressive treatment may result in fetal growth restriction (17,18).

While there is broad consensus that optimal glycaemic control enhances the prospects for the mother and child (19, 20), opinions differ on the agents necessary to achieve good glycaemic control. The other determinants of adverse pregnancy outcomes such as type of DM, age, parity, obesity, ethnicity, weight gain in pregnancy, smoking, alcohol use, co-existing disease states like hypertension and use of other medications in pregnancy also need to be taken into consideration (21-24).



### 2.1.1 Fetal outcomes

The adverse effects of diabetes in pregnancy on the fetus can be categorized in terms of when the events occur during the developmental period (25). Perinatal deaths result from events occurring in any trimester of pregnancy while spontaneous abortions and malformations are due to events occurring in the first trimester of pregnancy. Fetal macrosomia is largely a consequence of factors operating in the second and third trimesters of pregnancy. Third trimester events mainly determine the occurrence of polycythaemia, neonatal hypoglycaemia, neonatal jaundice, birth injuries, asphyxia and respiratory difficulties.

Whilst the considerable impact that treatment has on reducing perinatal mortaliy (PNM) has been well documented internationally, few such data have been reported from sub-Saharan Africa. In one study (26) with a PNM of 10%, perinatal deaths occurred in pregnancies with either poor glycaemic control or those that booked late and in yet another (27) the perinatal mortality was 26% in those pregnancies presenting less than 2 weeks to term compared with 6.1% in treated patients. The importance of timely and adequate care for the pregnant diabetic is further emphasized by the observation that a drop in PNM from 88.6% to 0% occurred with the introduction of a program of intensive care from pre-

conception to delivery compared with the period when no such program existed (28).

There are suggestions that the type of DM may impact on the occurrence of PNM. A number of studies have reported a higher PNM in type 2 DM compared with type 1 DM subjects (21,29). In one of these studies (21), the finding of a higher PNM in type 2 compared with type 1 DM patients was interesting because this occurred despite better glycaemic profiles in the type 2 DM cohort. Notwithstanding this, a multivariate logistic regression analysis showed high glycated haemoglobin (HbA1c) levels at admission and type 2 DM to be independently associated with PNM and major fetal anomalies. In the second study (29), the PNM in type 2 DM was 46.1 per 1000 compared with 8.9 per 1000 for GDM and 12.5 per 1000 for the type 1 DM and background non diabetic populations respectively. The type 2 subjects were however, significantly older, more obese and tended to present later than the type 1 DM subjects. A review of the "GDM" pregnancies showed that those with unrecognized type 2 DM subsequently diagnosed by the persistence of glucose intolerance post partum also had increased PNM compared with those with true GDM.

Diabetes is associated with an increased prevalence of fetal anomalies (30,31). Although the teratogenic mechanisms of DM are not clear, a role is suggested for hyperglycaemia, keto-acidosis, vascular abnormalities and oral hypoglycemic agents. The types of anomalies typically described in diabetic pregnancies largely involve the cardiovascular (CVS), skeletal and neurological systems. Cardiovascular malformations occurred in 3.6% of cases born to mothers with pre-existing DM compared with 0.7% of non-diabetic mothers (30). There are conflicting data on whether type 1 or type 2 diabetes subjects have a greater risk to anomalies. Becerra et al (31) reported a relative risk of 7.9% for major malformations among infants of mothers with type 1 DM compared with type 2 DM and relative risks of major central nervous system and CVS defects of 15.5% and 18.8% respectively. In contrast, Roland et al (32) found higher rates of congenital malformations in their type 2 DM compared with type 1 DM subjects, 12.3% vs 4.4%; p=0.002. Although the first trimester HbA1c was similar in both types of diabetes, multivariate analysis of the pooled group of type 1 or type 2 DM showed first trimester HbA1c to be independently associated with congenital malformations. The type 2 DM subjects in the cohort studied by Roland et al were also less likely to have pre-pregnancy counselling or to have folic acid supplementation in pregnancy.

An association between the severity of hyperglycaemia and fetal anomalies is suggested by the finding of 20.6 times risk for major CVS defects in GDM treated with insulin in the 3$^{rd}$ trimester compared with non insulin treated GDM. Multivitamin supplementation may reduce the occurrences of DM related fetal anomalies (33, 34). Wentzel et al (33) found lower rates of neural tube defects in the offspring of diabetic rats administered folic acid in comparison with those

that lacked folate supplementation. Similarly, Correa et al (34), in diabetic women also showed reduction in the risk of birth defects in offspring of mothers who used folic acid in the peri-conceptional period compared with those who did not. Indeed, the ADA and IDF recommend that women with diabetes be commenced on folic acid supplementation as an integral component of pre-conception care (4, 5).

The determinants of birth weight and macrosomia are the degree of glycaemia, maternal age, parity, pre-gestational body mass index (BMI), weight gain during pregnancy, multiple pregnancies, treatment modality and ethnicity. Birth weight and fetal macrosomia are related to several variables but mostly to the degree of glycaemia in pregnancy. A study of GDM subjects has shown the rates of macrosomia to be directly related to the 2-hour OGTT blood glucose levels (35). A positive association has also been shown to exist between birth weight and maternal weight gain during pregnancy (23). The relationship between ethnicity and birth weight is demonstrated by the finding of a macrosomia rate of 50% in Latino women compared with 19% in African-American women despite similar parity, BMI, weight gain and glycaemic control in pregnancy (36). A Scottish study (37) found higher birth weight and macrosomia rate in subjects with pre-gestational insulin treated DM compared to non-diabetic women. This Scottish study also observed that the macrosomia rate in the diabetic subjects was significantly inversely related to the duration of diabetes but positively associated with parity. Macrosomia was not associated with maternal height or smoking in this study.

### 2.1.2 Maternal outcomes

Pregnancy induced hypertension complicates 5-10% of all pregnancies in the United States of America and is a major cause of maternal, fetal and neonatal morbidity and mortality (38). There is an increased prevalence of hypertensive disorders in diabetic pregnancies (39). The increased incidence of pre-eclampsia may be related to insulin resistance (40,41), which has been described in the first trimester among women who subsequently developed pre-eclampsia (41). It was also associated with higher rates of conception aided by fertility drugs and elevated plasma glucose level at 1 hour post 75 gram OGTT. Nulliparity and advanced maternal age (42,43) are other factors that are associated with pregnancy-induced hypertension in GDM subjects.

There are many reports of higher caesarean section rates in diabetic pregnancies compared with non-diabetic pregnancies despite comparable macrosomia rates (44). This suggests that the diagnosis of diabetes in pregnancy may be the specific indication for caesarean section. There are however, data that this practice is not universal. A review of 216 GDM patients managed over a 9 year period found that the caesarean section rates for women with GDM and non GDM pregnancies were the same after adjustments for age and parity (45).

Another study (46) too showed comparable rates of caesarean section in GDM and normal pregnancies.

There is also an increased risk of urinary tract infection, hydramnios, and preterm delivery in diabetic pregnancies (47).

Gestational Diabetes Mellitus may not only recur, it is associated with an increased risk of subsequent occurrence of Type 2 DM (48-51). Predictive factors for the subsequent development of type 2 DM, include the diagnosis of GDM early in pregnancy, elevated FPG in pregnancy, need for insulin therapy during pregnancy, family history of DM, obesity, marked weight gain in pregnancy, recurrence of GDM, and ethnicity (46, 48). An extensive review (51) reported that raised FPG level during pregnancy is the risk factor most consistently associated with the subsequent development of type 2 DM. There is concern about the offspring of the diabetic mother as a higher occurrence of neurological and developmental disorders have been reported in such pregnancies compared with non-diabetic pregnancies (52). Furthermore, there may also be an increased risk of type 2 DM in the offspring of the GDM mother.

## 2.2 MANAGEMENT OF DM IN PREGNANCY

The aim of management of pregnancies complicated by diabetes mellitus as espoused by the Saint Vincent's declaration is "for a pregnancy outcome similar to that of non-diabetic pregnant women". The goal of treatment is to reduce/eliminate adverse maternal and fetal outcomes consequent upon the diabetic state to levels similar to that of non-diabetic women.

Target Glycaemic Levels: The difficulty in deciding on glycaemic goals is because the relationship between maternal glycaemia and perinatal risks is a continuous one (53-58). There is debate as to the blood glucose thresholds for various perinatal outcomes. Langer et al (17) showed that as mean blood glucose levels increased from: $\leq$ 4.8 mmol/l, 4.8-5.8 mmol/l, and $\geq$ 5.8 mmol/l, the incidence of large for gestational age and macrosomic infants increased. William et al (57) found a more than 2 fold risk of macrosomia with a mean plasma glucose $\geq$ 7.2mmol/l. On the other hand Sacks et al (54) did not find any meaningful glycaemic threshold value relative to birth weight or macrosomia. The risk of spontaneous preterm deliveries was reportedly increased with poor glycaemic control, a finding that was independent of perinatal complications that could have triggered early delivery (55). Based on available data, Langer suggested as shown in table i that glycaemic thresholds do exist for the various diabetic complications.

Table i: Glycaemic thresholds for fetal outcomes.

| Complication | Mean Glycaemic level (mmol/l) | HBA1C (%) |
|---|---|---|
| Macrosomia/LGA | 5.6 | - |
| Lung-maturation/Still birth | 6.1 | - |
| Congenital anomaly | 7.8 | < 13 |
| Spontaneous abortion | 8.9 | < 12 |

LGA: Large for gestational age

The glycaemic targets used by various practitioners vary but several are in agreement that FPG < 5.3 mmol/l is advised while FPG > 6.4 mmol/l is deleterious. The glycaemic goals recommended by the American Diabetes Association (ADA) in the management of GDM are pre-meal blood glucose levels below 5.3 mmol/l and one and two hour postprandial levels below 7.8 mmol/l and 6.7 mmol/l respectively (59). The glycaemic goals used at Grootte Schuur Hospital (GSH) maternal unit are FPG < 5.5 mmol/l and 2hour postprandial blood glucose levels < 6.7 mmol/l.

The modalities available for the treatment of DM in pregnancy are diet, exercise, OGLAs and insulin (60-63). The value of education is emphasized by the finding of a study (64) that reported an association between low functional health literacy in women with pre-gestational diabetes and several factors that may adversely impact on birth outcomes.

Diet remains the mainstay of treatment for diabetes in pregnancy. The ADA, caloric recommendation of 35 Kcal/kg of present pregnancy weight, has been critized due to concerns of postprandial hyperglycaemia (61). There are reservations of a hypocaloric diet. Although this diet is expected to more readily achieve normoglycaemia, it may be attained at the expense of ketosis, which may be harmful to the fetus (61,65). This fear is heightened by the demonstration of a near significant association (p=0.06) between poor psychomotor development scores in childhood and maternal plasma beta-hydroxybutyrate levels in the second and third trimesters (65). Ketonuria may however, develop in normal pregnancies after an overnight fast (9). A poor correlation between serum and urine ketones has been demonstrated by Coetzee et al (66). In this study, there was no ketonemia despite significant ketonuria. Furthermore, the diabetic subjects had similar rates of ketonuria irrespective of ingesting low or high calorie diets. Further, the neonates who were born to diabetic mothers with ketonuria had no increased incidence of fetal distress or asphyxia neonatorum.

A euglycaemic diet has therefore, been proposed at 30 kcal/kg per Pregnancy Weight (PPW) for BMI of 80-120% of ideal BMI, 24 kcal/kg PPW for BMI of 121-

150% of ideal BMI and 12 kcal/kg PPW for BMI ≥ 151% of ideal BMI; comprising of < 40% carbohydrate, ≥ 40% fat, 20% protein and < 800mg of dietary cholesterol/day and individualized according to patients' glycaemic levels (20,61). When diet fails to achieve glycaemic targets typically after 2 weeks of sole dietary therapy a decision must be made for add on therapy with either an OGLA or insulin. A high FPG was found to be predictive of poor response to sole dietary therapy (65); two-thirds of GDM patients with FPG > 5.3mmol/l failed to achieve good glycaemic control (MBG < 5.8 mmol/l, FBG < 5.8 mmol/l and 2-hour post-prandial < 6.7 mmol/l) when treated with diet therapy alone. In addition when FPG was > 6.4 mmol/l, only about a third achieved glycaemic targets on diet alone.

Exercise is desirable but the form it takes should not cause uterine contraction, fetal distress, fetal growth restriction or maternal hypertension (20,61). Upper arm ergometry meets these requirements and is thus the recommended form of exercise in pregnancy. Exercise in addition to diet has been shown to further significantly improve glycaemic control (67).

Insulin remains the standard pharmaceutical agent for glycaemic control in pregnancy. It is typically instituted where glycaemic targets are not achieved by diet and exercise. All diabetic women on insulin before pregnancy have insulin continued throughout pregnancy. The other factors besides FPG that predict a poor response to diet and oral agents and eventual recourse to insulin therapy in pregnancy include: hyperglycaemia on combined OGLAs, maternal obesity, multiple pregnancies and late booking. The average daily insulin requirements in pregnancy are: 0.7unit/kg body weight per day in the first trimester, 0.8unit/kg body weight per day in the second trimester and 0.9unit/kg body weight per day in the third trimester (61). Type 1 DM and insulin dependent type 2 DM women are usually administered 4 doses of insulin daily with pre-meal regular insulin and bedtime intermediate insulin. Type 2 DM and GDM patients requiring insulin may initially be commenced on bed time intermediate insulin eg, NPH 0.2 u/kg/day. If postprandial (PPG) glucose levels are elevated, rapid acting insulin may be administered, beginning with 1 unit of regular insulin per 10 g of carbohydrate per meal. Where both FPG and PPG are elevated, the patient may be converted to 4 injections per day. An intensified management approach is associated with enhanced perinatal outcome and in one study, the mean dose of insulin required to achieve near normoglycaemia was 91 units with an increase in insulin dosage occurring mainly between 24 and 30 weeks of gestation (68). The difference in the insulin requirements between non-obese and obese patients may be minimal (60). There may also be an advantage with the use of rapidly acting insulin analogues over regular insulin in pregnancy. Jovanovic (61) reported lower PPG levels with less hypoglycaemia when lispro-insulin and neutral protamine hagedorn (NPH) were used compared with a pre-meal regular insulin and bedtime NPH. Insulin aspart has also been reported to be safe in pregnancy with recommended optimal insulin dosage of 0.56 units/kg-body weight (59). The

long acting insulin analogue, glargine is however, not recommended for use in pregnancy.

The use of oral glucose lowering agents in pregnancy remains controversial in the international arena. Several OGLAs have been used in pregnancy but metformin and glibenclamide remain the current agents of choice. (62). Phenformin at doses greater than 0.1 mg/ml produced embryo lethality in mice. In addition, all embryos were killed at doses of 0.4 mg/ml, an association that did not occur with metformin. Phenformin has however, long been withdrawn from use because of its propensity to cause lactic acidosis. Metformin has proven efficacy in the management of anovulation associated with PCOS (69-73). In these studies, the rates of miscarriage were reduced with the use of metformin in early pregnancy. Furthermore, there were no deleterious perinatal outcomes even where it has been used before conception and throughout pregnancy. Follow up of offspring from women treated with metformin throughout pregnancy did not demonstrate any adverse effects on motor and social development at 3, 6 and 18 months of life (69,72). Metformin in combination with low calorie (1000 kcals/day) diet has been used at GSH in the management of GDM and type 2 DM in pregnancy especially in those who are obese, have PCOS or manifest other components of insulin resistance syndrome (74).

There is evidence that first generation sulphonylureas; tolbutamide and chlorpropamide cross the placenta (75). This may not be the case with later generation agents. The results of a randomized controlled clinical trial (RCCT) (76) comparing outcome in GDM treated with glibenclamide with those who were insulin treated has rekindled interest in the use of OGLAs in pregnancy. In this study, 404 women were randomly assigned to receive glibenclamide or insulin. The primary end point was achievement of target glycaemic goals while secondary end points included assessment of maternal and neonatal complications. The women enrolled either had a FPG $\geq$ 5.3 mmol/l but < 7.8 mmol/l on the day of OGTT or a FPG < 5.3 mmol/l on the day of OGTT but failed to achieve target glycaemic goals (FPG of 5.3 mmol/l and PPG of 6.7 mmol/l) after 2 weeks of dietary therapy. The mean blood glucose levels at study entry of 6.4 $\pm$ 1.1 mmol/l in the glibenclamide group and 6.5 $\pm$ 1.2 mmol/l in the insulin group dropped to 5.9 $\pm$ 0.9 mmol/l and 5.9 $\pm$ 1.0mmol/l respectively. Four percent of the glibenclamide group failed to achieve the primary goal of desired glycaemic targets. Importantly, the two treatment groups had comparable rates of macrosomia, hypoglycaemia, neonatal intensive care unit admissions and fetal anomalies. While the dosages of glibenclamide varied from 2.5mg to 20mg, it was not detectable in the cord serum of any infant. This has proven to be a landmark trial in the management of GDM, in that it provided the first RCCT evidence of equivalent outcomes with glibenclamide and insulin. Of note however, as only subjects with GDM diagnosed from 11 to 33 weeks of gestation were included, no inferences can be made on the teratogenicity of glibenclamide. The place of glibenclamide in glycaemic control in GDM may be limited to women

with milder degrees of glucose intolerance as suggested by the fact that the maximum daily dose of glibenclamide was 20 mg (twice the maximum dose of glibenclamide used in our unit) despite excluding women with FPG ≥ 7.8 mmol/l. It is however, reassuring that glibenclamide was not detectable in cord serum even at the high doses used. It is also quite conceivable that some of the subjects in this RCCT had undiagnosed type 2 DM as "GDM" diagnosed early in pregnancy is suggestive that undiagnosed DM preceded the index pregnancy (77). This cannot be confirmed as postnatal OGTT were not reported. Other studies (78,79) using the same inclusion criteria as Langer have found similar pregnancy outcomes in GDM pregnancies managed with glibenclamide or insulin. In one (78), 84% of subjects met the target glycaemic levels; ie mean blood glucose (MBG) of ≤ 5.8 mmol/l, FPG/Pre-meal blood glucose ≤ 5.3 mmol/l and 2-hour postprandial blood glucose ≤ 6.4 mmol/l. The majority of patients achieved target glyacemic levels with daily doses of glibenclamide ≤ 5 mg. Only 9.6% of subjects required daily doses of 15-20 mg to attain glycaemic control. High plasma glucose values at all time points during diagnostic GTT were major determinants of poor glycaemic control. When FPG at GTT was ≥ 6.1 mmol/l, 24% of women failed to respond to glibenclamide compared with a failure rate of 12% when FPG < 6.1 mmol/l. The other study (79) found that 80% of GDM dietary failures were effectively treated with glibenclamide and met strict glycaemic targets of FBG < 5.0 mmol/l and 1-hour PPG level of ≤ 7.5mmol/l. Only 8 of the 73 study subjects (11%) required daily doses of glibenclamide exceeding 7.5 mg to achieve glycaemic control. Indeed, it has been suggested that glibenclamide may be more cost effective than insulin (80).

It has been suggested that acarbose may be safe in pregnancy with comparable or better fetal outcomes compared with diet or insulin (81). The thiazolidinedione group of drugs is currently contraindicated for use in pregnancy due to paucity of data on its use in pregnancy (5).

There is extensive experience by the maternity unit of GSH with the use of metformin and glibenclamide in pregnancy (3, 9,10,82).



## 2.3 MONITORING IN PREGNANCY

### 2.3.1 Blood glucose monitoring

Glycaemic variables namely HBA1C, FPG and PPG are used either singly or in combination for blood glucose monitoring for people with diabetes. The HBA1C level reflects the mean level of glycaemia over the preceding 2-3 months while FPG and PPG reflect daily blood glucose control. Glycated haemoglobin levels have been shown to be lower in normal glucose tolerant pregnant women compared with age matched non-pregnant normal glucose tolerant women (83). The normal ranges of HbA1c using a Diabetes Control and Complications Trial (DCCT) aligned method were 4.7-6.3% in non-pregnant women, 4.5-5.7% in

early pregnancy and 4.4-5.6% in late pregnancy. The reduced HbA1c levels in pregnancy may be partly related to increased red cell turnover in pregnancy (84). The implication is that HbA1c levels in pregnancy reflect a shorter period of glycaemia during pregnancy compared with the non-pregnancy state. In addition it may not accurately reflect mean blood glucose results measured as FPG or PPG.

Self-monitoring of blood glucose (SMBG) provides the relevant data for guiding and assessing dietary and insulin therapy in pregnancies complicated by diabetes (85). It allows for early identification of diabetic patients requiring insulin and thus reduces the incidence of macrosomia (86). It also enhances patient education, facilitates lifestyle modification and allows women to actively participate in their care.

Debate continues on the superiority of pre-prandial versus post-prandial glucose measurement. A RCCT (87) reported significantly lower HBA1C (-3.0 ± 2.2 % versus –0.6 ± 1.6 %, $p<0.001$), lower birth weight (3469 ± 688 grams versus 3848 ± 434 grams, $p=0.01$), lower incidences of neonatal hypoglycaemia (3% versus 21%, $p=0.05$), large for gestational age (12% versus 42%, $p=0.01$), less delivery by caesarean section for cephalo-pelvic-disproportion (CPD) (12% versus 36%, $p=0.04$) in patients with glycaemic levels monitored post-prandially compared with those monitored pre-prandially despite being matched for pre-pregnancy weight, weight gain in pregnancy, GA at diagnosis of DM, GA at delivery, degree of compliance with treatment, and degree of target blood glucose concentration (pre-prandial values of 3.3-5.9 mmol/l and post-prandial value of < 7.8 mmol/l). The findings of De Veciana were confirmed by other workers (88) who showed that monitoring of non-fasting glucose levels rather than fasting levels are necessary to prevent macrosomia. While the ADA recommendation is for pre-meal blood glucose monitoring and additional PPG assessments where there is a disparity between mean pre-prandial plasma glucose levels and HbA1c (89) the International Diabetes Federation (IDF) (5) recommends that pre-breakfast and PPG levels be assessed together. The IDF recommendation is similar to that fourth international conference on GDM that emphasized the importance of pre-prandial and post-prandial blood glucose monitoring (90)

The suggested frequencies of monitoring with SMBG differ and range from 4-7 times per day (91). The ADA recommends at least 3 daily blood glucose measurements for insulin treated diabetic subjects. Those on OGLAs require fewer blood glucose assessments while the place of SMBG in diet alone treated subjects remains unclear. Kerssen et al (92) argue for more frequent blood glucose measurements as they found that more frequent measurements better reflected the fluctuations in blood glucose levels as it detected more hyperglycaemic and hypoglycaemic episodes in their cohort of type 1 DM women. This is despite similar glycaemic profiles assessed by HbA1c and mean

blood glucose levels irrespective of whether SMBG was done 4-5, 6-9 or ≥ 10 times daily.

### 2.3.2 Non-glycaemic parameters for monitoring

There is however, controversy regarding the adequacy of using glyacemic levels alone in the monitoring of DM in pregnancy. The need for non-glycaemic measures of diabetic control is evident in the fact that the complications of DM may occur despite meeting target glycaemic levels. The two commonly used methods are amniotic fluid insulin (AFI) and fetal anthropometric dimensions by ultrasonography. Their use however, may be limited as they would first have to become abnormal before an intervention is instituted (93).

## 2.4 GESTATIONAL DIABETES MELLITUS

This was defined by the ADA and the WHO as any degree of glucose intolerance with onset or first recognition during pregnancy (1,2). This definition is independent of the treatment modality during pregnancy or the persistence of glucose intolerance after pregnancy.

### 2.4.1 PREVALENCE OF GDM

Gestational diabetes mellitus occurs in 2-3% of all pregnancies (94) with differing prevalence rates in varying populations (95). This may be partly explained by an ethnic variation in insulin secretion and resistance (96). The diagnostic criteria also impacts on the prevalence of GDM in any given population (97,98). The high concordance between the prevalence of GDM and Type 2 DM (99-102) suggests a strong role for insulin resistance in the pathogenesis of GDM.

### 2.4.2 PATHOGENESIS OF GDM

Several workers have demonstrated insulin resistance in normal pregnancy (99-102). Insulin sensitivity may decrease by a factor of half in non-obese pregnant non-diabetic women (99). Although glucose tolerant women develop insulin resistance during the third trimester of pregnancy it is usually reversed post delivery and appears to be an adaptive mechanism to cope with the increased demands for growth of the growing fetus (100). It appears that women with GDM have a major beta cell defect that renders it impossible to compensate for their increased level of insulin resistance in late pregnancy (101). There have been arguments for the inclusion of GDM in the metabolic syndrome because of its association with other components of the metabolic syndrome (103). A role for free fatty acids, islet amyloid precursor peptide (IAPP), adiponectin and C-peptide in the pathogenesis of GDM has been explored by several workers (104-107). A contributory role for iron excess in the pathogenesis of GDM has been

suggested by studies showing raised serum ferritin levels in GDM compared with non-GDM patients matched for parity and BMI (108).

### 2.4.3 DIAGNOSIS OF GDM

#### 2.4.3.1 SCREENING FOR GDM

There is a wide variability in the diagnostic evaluation for GDM (109). The general practice is to identify existent risk factors for GDM in a particular population and to screen those who are positive for them. Risk factors for GDM include: advanced maternal age, maternal obesity, prior macrosomic infant, family history of diabetes, prior GDM, multi-parity, ethnicity, glycosuria, previous unexplained still births, fetal anomalies and hydramnios (110-118). Family history of diabetes in a first-degree relative, obesity and advanced maternal age have been identified as important risk factors for GDM. However, various screening criteria have different definitions for the same risk factors. While the ADA recommends screening when age is > 25 years (1) others have defined advanced maternal age as > 30 years or 35 years (113,115,117). Obesity is sometimes defined in terms of absolute weight (108,117) or BMI criteria, which may be variable (113,117). Macrosomia has been defined by Weight > 4000g (113), Weight >4500 kg (44) or weight > 95 percentile for gestational age (120). The impact of the varying definitions on the predictive capacity of these risk factors for GDM is not clear.

A number of studies support the arguments for universal rather than selective screening for GDM. Ostlund (110) found that traditional risk factors criteria as an indication to perform a 75 gram OGTT in the 28$^{th}$ to 32$^{nd}$ week of pregnancy only identified 29 of 61 women with IGT. The sensitivity of traditional risk factors as an indication to perform an OGTT was further reduced among primiparous compared with multiparous women. Indeed 50% of GDM patients may be missed if screened based on clinical criteria alone (121). Weeks et al (119) also found a 43% incidence of GDM in subjects without traditional risk factors for GDM, 28% of whom needed insulin treatment. The prospects to delay progression to type 2 DM by the institution of lifestyle measures (122) after delivery in women with GDM is yet another argument to support universal screening for GDM. The United States Preventive Services Task Force (111) position is however, that there is insufficient evidence to recommend for or against routine screening for GDM. This was based upon high rates of false positive screening results, variable glycaemic thresholds and inconsistency in screening protocols. In addition, there were no properly conducted randomized controlled trials that have examined the benefit of universal or selective screening compared with no screening.

### 2.4.3.2 DIAGNOSTIC CRITERIA FOR GESTATIONAL DIABETES MELLITUS

There is also no universal agreement on how to diagnose GDM (123). There is a wide variability in the diagnostic criteria used and even in the same country, practices differ (124). The more popular criteria are those of the World Health Organization (WHO) (2) and the ADA (1). Both criteria have undergone several revisions over years.

The WHO criteria for the diagnosis of DM first came into being in 1979 and have undergone revisions in 1980, 1985 and 1999.

The 1980 WHO criteria (125) for the diagnosis of GDM using venous plasma glucose values were a FPG ≥ 8.0 mmol/l and or 2hour plasma glucose value, post 75 grams OGTT ≥ 8.0 mmol/l. A distinction was made between DM and IGT. DM was diagnosed with a FPG ≥ 8.0 mmol/l and or 2hour plasma glucose level, post 75 grams OGTT ≥ 11.0 mmol/l while IGT was diagnosed with FPG < 8.0 mmol/l and 2hour plasma glucose level, post 75 grams OGTT of ≥ 8.0 mmol/l < 11.0 mmol/l.

The 1985 WHO criteria (126) for the diagnosis of GDM using venous plasma glucose values was a FPG ≥ 7.8 mmol/l and or 2hour plasma glucose level, post 75 grams oral glucose load ≥ 7.8 mmol/l. Similar to the 1980 criteria, the distinction between DM and IGT was retained. DM was diagnosed with a FPG ≥ 7.8 mmol/l and or 2hour plasma glucose level, post 75 grams OGTT ≥ 11.0 mmol/l while IGT was diagnosed with FPG < 7.8 mmol/l and 2hour plasma glucose level, post 75 grams OGTT of ≥ 7.8 mmol/l but less than 11.0 mmol/l.

The 1999 WHO criteria (2) for the diagnosis of GDM were similar to those of 1980 and 1985 in that venous plasma glucose levels and the use of 75 grams OGTT were recommended. It differed from the previous criteria in that no distinction was made between IGT and DM in pregnancy. The FPG level was lowered to 7.0 mmol/l while the 2hour plasma glucose level, post 75 grams OGTT cut off was 7.8 mmol/l. Thus GDM by the 1999 criteria was diagnosed with a FPG ≥ 7mmol/l and or 2hour plasma glucose level, post 75 grams OGTT ≥ 7.8 mmol/l.

The argument advanced for the use of the WHO criteria is that it has universal acceptance and applicability and allows for comparison of glucose tolerance in pregnant and non-pregnant subjects (123). The concerns with the WHO criteria, which were reached by consensus, are that it has not been validated in pregnancy and that it neither predicts the occurrence of maternal and fetal outcomes in pregnancy nor the subsequent risk of development of diabetes in the mother after pregnancy (123).

There are however, modifications of the WHO diagnostic criteria for GDM in an attempt to improve its sensitivity and specificity and to allow for risk stratification. The European consensus on the WHO 75 gram OGTT (127) similar to the 1980 and 1985 WHO criteria made a distinction between IGT and DM since these represent varying degrees of glucose intolerance with potentially varying impact on pregnancy outcomes: Normal Glucose tolerance: FPG < 6.7 mmol/l and 2hour OGTT plasma glucose value of < 9 mmol/l, Impaired Glucose Tolerance (IGT): FPG < 6.7 mmol/l and 2hour OGTT plasma glucose value of 9-11 mmol/l, DM: FPG ≥ 6.7 mmol/l, and or 2hour OGTT plasma glucose value of ≥ 11 mmol/l. The Australasian criteria for the diagnosis of GDM (128) are a FPG ≥ 5.5 mmol/l and or a 2hour OGTT plasma glucose value of ≥ 8.0 mmol/l. Once again, these threshold values have been reached by consensus (47). The higher post glucose load threshold values for IGT in the European and Australasian modifications of the WHO criteria were to allow for glucose intolerance that characterizes late pregnancy.

The diagnostic criteria used in the United States for the diagnosis of GDM are at variance with the WHO criteria. In 1979, the National Diabetes Data Group (NDDG) revised the original O'Sullivan and Mahan criteria, converting whole blood values to plasma values that were subsequently adopted by the ADA and ACOG. The recent ADA criteria for the diagnosis of GDM are based on any 2 plasma glucose values ≥ the threshold values following a 3hour, 100 gram OGTT, after an initial screening test. The need for a diagnostic test is borne out by the poor predictive value of the 1hour post 50 gram oral glucose challenge test (111,121,129). A positive predictive value of 39.2% to 51.6% has been shown for the 50 gram glucose challenge test based on a cut value of 7.8 mmol/l depending on whether the 100 gram full OGTT was interpreted by the National Diabetes Data Group, Carpenter and Coustan or Sacks criteria (table b) (129). A caveat is that the predictive value of a screening test is dependent on the prevalence of disease in that population. The O' Sullivan and Mahan criteria were based on its ability to identify mothers at risk for developing DM post delivery (127). They do not predict maternal and fetal complications of GDM. The 100 gram OGTT is however, interpreted by various criteria as shown in the table below.



Table ii. Various Interpretations of the 100 gram OGTT.

| | Fasting plasma glucose(mmol/l) | 1Hour Plasma Glucose Post OGTT(mmol/l) | 2Hour Plasma Glucose Post (mmol/l) | 3Hour Plasma Glucose Post OGTT(mmol/l) |
|---|---|---|---|---|
| NDDG | 5.8 | 10.5 | 9.1 | 8.0 |
| C&C | 5.2 | 9.9 | 8.6 | 7.7 |
| Sacks et all | 5.3 | 9.5 | 8.4 | 7.2 |

NDDG: National Diabetes Data Group, C&C: Carpenter and Coustan.

Numerous concerns have been expressed about the O'Sullivan and Mahan criteria such as its derivation from a mixed racial and socio-economic population,

that the criteria did not relate the significance of the various plasma glucose levels to pregnancy outcome, obesity was not considered as a confounding variable and the 100 gram glucose load frequently caused nausea and vomiting (47). The interpretation of the 100 gram GTT also gives various sensitivities and specificities (130) for the diagnosis of DM.

The ADA sponsored 4th International Workshop Conference on GDM (90) recommended the use of either the 100-gram or 75 gram oral glucose tolerance test in the diagnosis of GDM. While the 100 gram OGTT assesses the FPG; 1,2,3 hour post glucose load plasma glucose values; the 75 gram OGTT assesses the FPG, 1 and 2 hour post glucose load plasma glucose values, with similar cut off values as the 3 hour post 100 gram OGTT as shown below.

Table iii. 100 gram and 75 gram OGTT threshold values as recommended by the ADA 4th International Workshop Conference on GDM.

| | Fasting plasma glucose(mmol/l) | 1Hour Plasma Glucose Post OGTT(mmol/l) | 2Hour Plasma Glucose Post OGTT(mmol/l) | 3Hour Plasma Glucose Post OGTT(mmol/l) |
|---|---|---|---|---|
| 100 g OGTT | 5.3 | 10.0 | 8.6 | 7.8 |
| 75 g OGTT | 5.3 | 10.0 | 8.6 | - |

A patient may be diabetic based on one set of criteria and be non-diabetic by another set of criteria. A head-to-head comparison of the WHO and recommendations of the 4th International Workshop have found the WHO criteria more sensitive for the diagnosis of DM; 81% vs 59% but less specific 76% vs 91% (131). This is similar to the finding of other workers (47,132).

The controversy in the diagnosis of GDM is a result of the continuous relationship between maternal glycaemia and macrosomia related perinatal risks (27). There can be no proof of a superior set of diagnostic criteria based on maternal plasma glucose values alone unless a biological threshold of risk can be established. This controversy is further compounded by the poor reproducibility of GTT results. This indeed has been observed in the maternity unit of the GSH, where patients with risk factors for GDM meet the criteria for GDM at one visit and revert to normal glucose tolerance on subsequent retesting; thus the practice by the unit to treat patients based on the results of plasma glucose profile and not the OGTT result (Coetzee, personal communications). There is hope that the controversy surrounding the diagnostic plasma glucose criteria for GDM will be resolved with the results of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study (133) to be reported in 2007.

There is also a lack of consensus on the timing of screening for GDM. Data to support specific time for screening are sparse. Diagnosis of GDM early in pregnancy may be indicative of patients with severe GDM or unknown pre-gestational diabetes (134). Some workers have therefore advocated for early

screening in high-risk populations (77,135). Early diagnosis may also permit prompt intervention with prospects for improved perinatal outcome (77). Later screening identifies more people with GDM but with lower maternal-fetal risks. The recommendation of the ADA and the WHO is to screen all with risk factors for GDM at booking with a repeat at the $24^{th}$ to $28^{th}$ week of pregnancy. A one step approach; i.e. proceeding straight to a full OGTT may be cost effective in high-risk individuals but a 2 step approach is recommended for low risk populations by the ADA. The 50 gram 1 hour GCT has been noted to be poorly predictive of GDM (111,121). The USPTF (111) notes that fewer than 20% women with a positive glucose challenge test (GCT) will meet the criteria for GDM on full OGTT. There is a positive predictive value of 63-66% for GDM with an increase in threshold values from 7.8 mmol/l to 14.4 mmol/l depending on whether OGTT values are interpreted by NDDG or CC criteria (121).

There has been controversy on the extent of benefits in treating GDM particularly gestational IGT. Although a study (136) had found comparable PNM and morbidity indices regardless of whether IGT was treated, several others (137-141) reported benefit in reducing perinatal morbidity but not mortality in treated IGT subjects when compared with untreated IGT or normal pregnancies. These studies were however, non-randomized in design. Indeed the USPTF position against treating GDM was based on the premise that there was no evidence that treatment of GDM was beneficial from randomized studies. The USPTF noted that adverse outcomes such as macrosomia and shoulder dystocia were more common in pregnancies uncomplicated by GDM. Moreover, risk factors such as obesity and advanced maternal age for the adverse events seen in pregnancy were prevalent in the general population. This position may change following the publication of the ACHOIS trial (7), the first randomized trial examining the benefits of treating gestational IGT. This demonstrated a significant reduction in a composite measure of perinatal death, shoulder dystocia, bone fracture and nerve palsy in subjects who were intensively treated compared with those who received routine care. Indeed, there was no significant difference between the PNM of intensively vs routinely treated subjects although there was a trend towards a significant reduction in the intensively treated group ($p=0.06$). A subsequent editorial (6) recommended universal screening for all pregnant women and mandated all maternity service providers to ensure that adequate resources are allocated to the detection and treatment of GDM. This recommendation may be difficult to implement in poor economies.

## Chapter 3. Design, Subjects, Methods

### 3.1 Design

We conducted a retrospective analysis of the perinatal outcomes of pregnant subjects with types 1 and 2 DM who delivered at GSH, a tertiary health care facility in Cape Town, from 1991 to 2000. A similar analysis was done on GDM subjects who delivered at GSH from 1995 to 1997. The Peninsula Maternal and Neonatal Service (PMNS) is the drainage area to GSH for the entire primary and secondary obstetric public sector in Cape Town. The PMNS delivers about 30,000 pregnancies annually and has an overall PNM rate of 30 per 1000 (3).

### 3.2 Subjects

Women with type 1 DM, type 2 DM and GDM who had singleton pregnancies reaching 24 weeks of gestation were included.

### 3.3 Methods

The case records of eligible subjects were reviewed after ethical approval was obtained from the institutional ethics committee. Demographic data, measures of glycaemic control, mode of therapy, pregnancy outcome variables were collected.

Demographic data abstracted were: maternal age, parity, BMI at booking, gestational age at booking and the duration of diabetes for subjects with pre-gestational diabetes.

Pregnancy outcomes assessed were: birth weight and rates of PNM, fetal anomaly, caesarean section, neonatal hypoglycaemia, macrosomia, neonatal jaundice and pre-eclampsia.

Glycaemic control was assessed using mean fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated haemoglobin (HbA1c) levels. This was calculated for each trimester. The blood glucose levels were measured on samples collected by the patient over the 24 hours preceding antenatal clinic visits. The FPG levels represented the pre-breakfast blood glucose measurements. The PPG levels were the average of blood glucose profiles done after breakfast, lunch and supper.

All insulin treated women were encouraged to perform self-monitoring of blood glucose (SMBG). This consisted of measurements done on capillary blood obtained at 06h00, 11h00, 14h00, 20h00 and at 3h00 particularly in women with type 1 DM. Breakfast, lunch and supper were eaten at 8h00, 12h00 and 17h00 respectively. In addition snacks were served at 10h00, 14h00, 19h00 and at

22h00. The frequencies of measurements were guided by the degree of glycaemic control. The women kept a diary of blood glucose readings and the doses of insulin administered. Periodic measurements were done in the hospital on blood samples collected by the patients at home. This allowed for comparison of the results obtained by the patients at home with that measured in the hospital laboratory.

### 3.4 Routine Clinical Management at GSH maternity unit

#### 3.4.1 Pre-gestational Diabetes

Women with pre-gestational type 1 or 2 DM were referred to the GSH maternity unit when pregnant and admitted to a single antenatal ward for review. This included assessment of gestational age, diabetes education and management of glycaemia. During the admission, which lasted for about 2-4 days, the patients were educated on diabetes and pregnancy, instructed on SMBG, recognition and treatment of hypoglycaemia and insulin injection techniques. They were placed on a diet of about 1600kcal/day distributed into the 3 main meals and 4 snacks taken between the meals and at bedtime.

All type 1 and 2 DM women already on insulin before pregnancy had their pre pregnancy regimen and doses of insulin discontinued. They were then placed on a sliding scale insulin regimen based on body weight (table iv) with regular insulin (actrapid, Novo Nordisk) 3 times daily before meals and isophane insulin (protaphane, Novo Nordisk) nocte at bedtime. The doses of regular insulin during sliding scale therapy were adjusted according to blood glucose readings obtained at 07h30 (pre breakfast), 11h30 (pre lunch) and 16h30 (pre supper) while that of isophane was based on blood glucose levels at 21h30 (pre bedtime snack). After 48 hours, they were converted to a fixed dose regimen of regular insulin pre-prandially and intermediate insulin at bedtime. The doses in the fixed dose regimen were calculated using the following formula; all the doses of insulin (regular insulin and isophane insulin) administered over the 48-hour period of sliding scale insulin therapy were totaled and 10 units empirically added. This was then divided by 2 to arrive at the 24hour (daily) insulin doses. The calculated daily insulin dose was further divided by 3 to obtain premeal insulin dosage. The bedtime dose of isophane insulin was derived by dividing premeal insulin dose by 3. The premeal doses of regular insulin and bedtime isophane insulin insulin were subsequently adjusted based upon PPG and FPG levels respectively until glycaemic control was achieved. Additional blood glucose measurement was done at 3h00 to enable the ascertainment of a fasting hyperglycaemia as due to somogyi or dawn phenomenon. The HbA1c levels were done on an average of once to twice per trimester. The target blood glucose levels were FBG < 5.5 mmol/l, 2hour PPG < 6.7 mmol/l and HBA1C < 7%.

Table iv Antenatal sliding scale regimen

| Blood glucose level (mmol/l | Maternal weight <60kg | 60-90kg |
|---|---|---|
| **Antenatal sliding scale for regular insulin** | | |
| <4 | 0 | 0 |
| 4.1-6.0 | 4 | 6 |
| 6.1-8.0 | 8 | 12 |
| 8.1-10.0 | 12 | 18 |
| 10.1-12.0 | 16 | 24 |
| >12.0 | 24 | 30 |
| **Antenatal sliding scale for isophane insulin** | | |
| <6.0 | 0 | 0 |
| 6.1-8.0 | 4 | 6 |
| 8.1-10.0 | 8 | 12 |
| 10.1-12 | 12 | 18 |
| ≥12 | 16 | 24 |

* Although this was the prescribed regimen, low insulin doses *were* given at blood glucose levels below 4 mmol/l and 6 mmol/l respectively, together with an additional snack.

Type 2 DM subjects who were previously not on treatment or on diet alone, first had blood glucose spreads done at booking. The commencement of OGLAs or continued use of diet alone was based on a FPG < 5.5 mmol/l and all 2hour PPG levels < 6.7 mmol/l. Those initially treated with diet were given OGLAs if glycaemic targets were not met. Metformin and glibenclamide were the only OGLAs used in the unit. Obese patients particularly those with features of insulin resistance and PCOS were commenced on metformin. Glibenclamide was the choice for non-obese subjects. Type 2 DM women already on OGLAs other than glibenclamide and metformin such as gliclazide and chlorpropamide had these agents discontinued at booking. Those on doses of metformin and glibenclamide exceeding the maximum used in the unit had them reduced. Metformin was usually started at a dose of 850 mg daily while glibenclamide was commenced at 2.5 mg daily. The maximum doses of metformin and glibenclamide used in the unit were 1700 mg and 10 mg respectively. Combined metformin and glibenclamide were prescribed if glycaemic goals had not been attained on monotherapy. Patients were converted to insulin where glycaemic targets were not achieved on combined metformin and glibenclamide therapy. The dose of insulin was then adjusted until target glycaemic control was achieved. The indications for insulin therapy in type 2 DM subjects other than insulin treatment before pregnancy and failure of combined OGLAs therapy included FPG ≥ 8.0 mmol/l and late booking.

Patients with hypertension were treated with methyldopa as the preferred anti-hypertensive agent with add on nifedipine therapy as indicated. Other anti-hypertensives particularly diuretics, angiotensin converting enzyme inhibitors, angiotensin 2 receptor blockers and beta-blockers were discontinued.

Patients were reviewed at the antenatal clinic fortnightly till 32 weeks, and thereafter, weekly, until delivery. Routine ultrasound scans were done at 12, 22, 32 and 36 weeks to assess fetal growth and exclude fetal anomalies. Patients were routinely re-admitted at 32 weeks for re-evaluation. They may however, have been re-admitted at any time in the course of gestation if indicated. Delivery was usually timed for 38 weeks gestational age.

Oral glucose lowering agents and insulin injections were withdrawn 24 hours before elective delivery and the patient commenced on an insulin glucose infusion at the rate of 1 iu of insulin and 5 grams of glucose per hour. The rate of insulin-glucose infusion was adjusted to achieve and maintain target glycaemic goals. The infusion was stopped immediately after delivery. Subsequent treatment was determined by blood glucose spreads post delivery. A 48-hour postnatal sliding scale insulin therapy using the regimen in table v guided further insulin therapy in women with type 1 DM. The total doses of insulin administered over the 48 hour of sliding scale insulin therapy was totaled and divided by 2 to arrive at 24 hour (daily) requirements and subsequently administered as biphasic insulin (actraphane 30/70, Novo Nordisk), twice daily before breakfast and supper, in a ratio of 2:1 respectively.

Table v: Postnatal insulin sliding scale regimen

| Blood glucose level (mmol/l | Maternal weight <60kg | 60-90kg |
|---|---|---|
| **Postnatal sliding scale for regular insulin** | | |
| <6 | 0 | 0 |
| 6.1-8.0 | 4 | 6 |
| 8.1-10.0 | 8 | 12 |
| 10.1-12.0 | 12 | 18 |
| >12.0 | 16 | 24 |
| **Postnatal sliding scale for isophane insulin** | | |
| <6.0 | 2 | 3 |
| 6.1-8.0 | 4 | 6 |
| 8.1-10.0 | 8 | 12 |
| 10.1-12 | 12 | 18 |
| ≥12 | 16 | 24 |

Babies were assessed after delivery by a paediatrician to exclude malformations and macrosomia. They were subsequently observed over a 24hour period for hypoglycaemia, hyperbilirubinemia and respiratory distress.

3.4.2 Gestational Diabetes

Non-diabetic pregnant women, attending primary and secondary health centers in the drainage areas of GSH were routinely screened for diabetes if they have 2 or more of the following risk factors for DM; family history of DM in 1$^{st}$ degree relative, obesity, glycosuria, previous macrosomic baby, previous unexplained perinatal loss and previous GDM. The initial test was a 75gram OGTT done in the community health center. Those with a positive test were referred to GSH maternity unit for a repeat OGTT. Patients presenting before 24 weeks of gestation with a negative result (i.e. normal glucose tolerance test) had a repeat GTT between the 24$^{th}$ and 28$^{th}$ week of gestation. Initial screening was done as early as possible after 12 weeks because of concern of a high prevalence of occult pregestational diabetes in the community.

The diagnosis of GDM and subsequent classification as DM or IGT was based on the 1985 WHO criteria: DM was diagnosed with FPG ≥ 7.8 mmol/l and or 2hour OGTT plasma glucose level of ≥ 11.0 mmol/l while that of IGT was based on FPG < 7.8 mmol/l and 2hour OGTT plasma glucose level of ≥7.8 mmol/l and < 11.0 mmol/l. The women diagnosed with GDM were subsequently managed using the same protocol as for the type 2 DM subjects.

3.5 Classification of pre-gestational and GDM treatment groups

Subjects with type 2 DM subjects were categorized into 3 different groups to allow an assessment of the impact of treatment modality on maternal and perinatal outcomes.The type 2 DM subjects in this report were categorized into 3 treatment groups based on treatment in pregnancy: group 1; only OGLAs, group 2; converted from OGLAs to insulin, group 3; only diet/insulin. The type 1 DM subjects served as a "control" group for the pre-gestational type 2 DM subjects.

The GDM subjects were categorized as DM or IGT based on screening FPG and the 2hour 75gram OGTT plasma glucose levels using the 1985 WHO criteria for the diagnosis of GDM (126). The GDM subjects were classified based on treatment in pregnancy into 4 treatment groups: group 1; only diet, group 2; only OGLAs, group 3; converted from OGLAs to insulin, group 4; only insulin. The IGT subjects were further stratified into 2 groups based on the diagnostic FPG; < 5.5 mmol/l and ≥ 5.5 mmol/l or 2 hour OGTT plasma glucose level EASD criteria for GIGT; < 9.0mmol/l and ≥< 11.0 mmol/l. The categorization and subsequent stratification of IGT subjects was to allow the examination of the impact of

treatment modality in our GDM and the effect of stratification of IGT subjects on maternal and perinatal outcomes.

3.6 Definitions

OGLAs only treated: Managed with only OGLAs throughout pregnancy and received supervised care at GSH maternity unit for a minimum period of 4 weeks during pregnancy.

OGLAs to insulin treated: Managed with OGLAs initially in the course of pregnancy but subsequently changed to Insulin. Patients received supervised care at GSH maternity for a minimum period of 4 weeks during pregnancy.

Diet/insulin only treated: Managed with only insulin and or diet in the course of pregnancy; limited to patients who were only on diet or insulin therapy before pregnancy and received care at GSH Maternity unit for a minimum period of 4 weeks during pregnancy.

PNM (per 1000 births): Stillbirth of a fetus weighing ≥ 500 grams and neonatal death within 7 days of birth.

Macrosomia: Birth Weight of at least 4000 grams regardless of gestational age at delivery.

Neonatal hypoglycaemia: Blood glucose < 2.2 mmol/l.

Fetal anomaly: As defined by Becerra et al (31), however, patent ductus arteriosus was not considered a malformation irrespective of gestational age or birth weight at delivery.

Polycythaemia: Packed cell volume ≥ 60%

Neonatal jaundice: Hyperbilirubinaemia usually requiring phototherapy.

Respiratory difficulties: Any form of respiratory discomfort or assistance including the use of facemask oxygen.

Untreated: Receiving less than 4 weeks of supervised care at GSH.

3.7 Statistical analysis

Results are expressed as Mean ± S.E.M. Group means were compared by analysis of variance with a Bonferroni correction where necessary and Chi Square test as appropriate. Univariate and multivariate logistic regression analysis was performed to determine the predictors of poor fetal outcomes. The level of

statistical significance was taken as $P < 0.05$. The statistical package used was statistica version 7.

# CHAPTER 4: RESULTS

## 4.1 Pre-gestational diabetes: types 1 and 2 DM subjects

There were 578 pregnancies in pre-gestational diabetic women over the 10 year period from 1991 to 2000; 197 in type 1 and 381 in type 2 DM subjects. The type 1 DM subjects consisted of 23.9% black Africans, 66.5% of mixed ancestry and 9.6% white women. The population of the type 2 DM subjects was similar to that of type 1 DM subjects, consisting of 35.7% black Africans, 63.1% of mixed ancestry and 1.2 % white women.

### 4.1.1 Comparison of treated types 1 and 2 DM subjects

Table 1a: Demographic indices of treated types 1 and 2 DM subjects.

| | Type1 DM N=171 | Type 2 DM. N=338 | P value |
|---|---|---|---|
| Maternal age (years) | 27.7 ± 0.4 | 33.3± 0.3 | P < 0.05 |
| Booking GA (weeks) | 15.7± 0.6 | 17.5± 0.4 | P < 0.05 |
| Parity (no) | 2.5± 0.1 | 3.8± 0.1 | P < 0.05 |
| Booking BMI (kg/m$^2$) | 28.2± 0.5 | 32.6±0.4 | P < 0.05 |
| Duration of DM (years) | 9.0± 0.4 | 4.4± 0.3 | P < 0.05 |

Demography (table 1a): The treated type 1 DM patients were younger, of lower parity and booked earlier than the treated type 2 DM patients. The former had a longer duration of DM than the latter. The type 1 DM patients had a lower BMI than the type 2 DM patients. While the former were overweight at booking the latter were obese.

Table 1b: Glycaemic profiles of treated types 1 and 2 DM subjects.

| | Type1 DM N=171 | Type 2 DM. N=338 | P value |
|---|---|---|---|
| Booking HBA1C (%) | 7.8± 0.2 | 7.4± 0.3 | P=0.06 |
| Proportion (%) with booking HbA1c > 7% | 59.3 | 55.4 | P=0.4 |
| 2nd Trimester Glycaemic levels | | | |
| HBA1C (%) | 6.7± 0.2 | 6.5± 0.1 | P=0.4 |
| FPG (mmol/l) | 6.3±0.1 | 5.9±0.1 | P<0.05 |
| PPG (mmol/l) | 6.3±0.1 | 6.4±0.1 | P=0.9 |
| 3rd Trimester Glycaemic levels | | | |
| HBA1C (%) | 6.4± 0.2 | 6.2± 0.1 | P=0.3 |
| FPG (mmol/l) | 5.5±0.1 | 5.4±0.1 | P=0.6 |
| PPG (mmol/l) | 6.0±0.1 | 6.3±0.1 | P<0.05 |
| Last HbA1c (%) | 6.5±0.1 | 6.3±0.1 | P=1.0 |
| Proportion (%) with last HbA1c > 7% | 34.5 | 32.9 | P=0.8 |

Glycaemic profiles (table 1b): The HbA1c levels at booking tended to be higher in the type 1 than the type 2 DM subjects but were similar in both types of DM subjects for the rest of gestation. More than 50% of the type 1 DM or type 2 DM subjects had a booking HbA1c > 7%. The type 1 DM subjects had a significantly higher 2nd trimester FPG but lower 3rd trimester PPG level than the type 2 DM subjects. The HbA1c though high at booking, were within target goals in the 3rd trimester yet a third of both groups still had HbA1c levels > 7%.

Table 1c: Pregnancy outcomes of treated types 1 and 2 DM subjects.

| | Type1 DM N=171 | Type 2 DM. N=338 | P value |
|---|---|---|---|
| Birth weight (grams) | 3066.3± 64.5 | 3257.9± 45.4 | P<0.05 |
| Perinatal mortality (per 1000) | 67.1 | 35.9 | P<0.05 |
| Fetal anomaly rate (%) | 2.3 | 1.5 | P=0.5 |
| Caesarean section rate (%) | 63.0 | 59.8 | P=0.5 |
| Neonatal hypoglycaemia rate (%) | 13.1 | 19.3 | P=0.2 |
| Macrosomia rate (%) | 11.6 | 18.7 | P=0.04 |
| Pre-eclampsia rate (%) | 4.1 | 1.9 | P=0.1 |
| Neonatal jaundice rate (%) | 16.9 | 11.7 | P=0.2 |
| Polycythaemia (%) | 1.5 | 0.7 | P=0.4 |
| Respiratory difficulties | 25.4 | 19.3 | P=0.2 |
| Urinary tract infection (%) | 10.6 | 4.3 | P=0.007 |
| Hydramnios (%) | 2.4 | 3.1 | P=0.6 |
| Proteinuria (%) | 7.7 | 3.9 | P=0.08 |
| Ketonuria (%) | 1.2 | 0.6 | P=0.5 |



Pregnancy outcome (table 1c): The PNM was about 2 fold greater in treated type 1 compared with treated type 2 DM subjects. The birth weight and macrosomia rate were higher in type 2 than type 1 DM subjects. The rates of fetal anomaly, caesarean section, pre-eclampsia, hydramnios, ketonuria polycythaemia, neonatal hypoglycaemia and jaundice were comparable. Proteinuria rate showed a trend towards a significant increase in type 1 DM subjects, who also had a significantly greater rate of urinary tract infection.

### 4.1.2 Comparison of treated versus untreated type 1 DM subjects

Table 2a: Comparison of demographic and glycaemic profiles of treated and untreated type 1 DM subjects.

| | Treated N=171 | Untreated N=26 | P value |
|---|---|---|---|
| Maternal age (years) | 27.7± 0.4 | 28.4± 1.2 | P=0.6 |
| Booking GA (weeks) | 15.7± 0.6 | 23.1± 1.8 | P<0.05 |
| Parity (no) | 2.5± 0.1 | 3.2± 0.3 | P=0.05 |
| Booking BMI (kg/m$^2$) | 28.2± 0.5 | 29.7±1.5 | P=0.4 |
| Duration of DM (years) | 9.0± 0.5 | 10.0± 1.5 | P=0.5 |
| Booking HBA1C (%) | 7.8± 0.2 | 8.6± 0.6 | P=0.2 |
| Proportion (%) with booking HbA1c > 7% | 59.3 | 68.8 | P=0.5 |
| Last HBA1C (%) | 6.5± 0.2 | 8.3± 0.5 | P<0.05 |

There were 26 untreated and 171 treated type 1 DM women. The majority in both groups were of mixed ancestral origin. The maternal ages, BMI at booking and duration of DM were comparable in both groups. The untreated group had a higher parity and booked later than treated type 1 DM patients. Booking HbA1c levels were comparable although the untreated booked later than the treated. The last HbA1c level before delivery was however; lower in the treated group compared with the untreated group.

Table 2b: Pregnancy outcomes of treated versus untreated type 1 DM subjects.

| | Treated N=171 | Untreated * N=26 | P value |
|---|---|---|---|
| Birth weight (grams) | 3066.3± 64.5 | 2614.2± 252.9 | P=0.09 |
| Perinatal mortality (per 1000) | 67.1 | 500 | P<0.05 |
| Fetal anomaly rate (%) | 2.3 | 25 | P<0.05 |
| Caesarean section rate (%) | 63.0 | 25.0 | P=0.6 |
| Macrosomia rate (%) | 11.6 | 16.7 | P=0.6 |
| Pre-eclampsia rate (%) | 4.1 | 0.0 | P=0.4 |
| Urinary tract infection (%) | 10.6 | 5.6 | P=0.5 |
| Hydramnios (%) | 2.4 | 0.0 | P=0.5 |
| Proteinuria (%) | 7.7 | 5.3 | P=0.7 |
| Ketonuria (%) | 1.2 | 0.0 | P=0.6 |

Pregnancy outcome (table 2b): * Data on fetal outcomes in the untreated group was only available in 12 cases. In these, there were high rates of major adverse events. The PNM and fetal anomaly rates were 7 fold and 10 fold higher respectively in the untreated than the treated group. Birth weight, tended to be lower in untreated type 1 DM subjects.

### 4.1.3 Comparison of treated versus untreated type 2 DM subjects

Table 3a: Comparison of demographic and glycaemic profiles of treated and untreated type 2 DM subjects.

| | Treated N=338 | Untreated N=43 | P value |
|---|---|---|---|
| Maternal age (years) | 33.3± 0.3 | 35.0± 0.7 | P <0.05 |
| Booking GA (weeks) | 17.5± 0.5 | 27.4±1.2 | P <0.05 |
| Parity (no) | 3.8± 0.1 | 4.2± 0.2 | P = 0.2 |
| Booking BMI (kg/m$^2$) | 32.6± 0.4 | 35.5±1.0 | P <0.05 |
| Duration of DM (years) | 4.1± 0.6 | 4.4± 0.2 | P = 0.7 |
| Booking HBA1C (%) | 7.4± 0.1 | 7.5± 0.4 | P=0.7 |
| Proportion with booking HbA1c > 7% | 55.4 | 55.2 | P=1.0 |
| Last HBA1C (%) | 6.3± 0.1 | 7.5± 0.3 | P<0.05 |

Demography: (table 3a): The treated group were younger and had a lower BMI than the untreated group. Both groups were, however, obese and had similar parity and durations of DM. The booking HbA1c was comparable in both groups but booking was later in the untreated group. The last HbA1c level was lower in the treated group compared with the untreated group.

Table 3b: Pregnancy outcomes of treated versus untreated type 2 DM subjects.

| | Treated N=338 | Untreated* N=43 | P value |
|---|---|---|---|
| Birth weight (grams) | 3257.9± 47.2 | 3186.0± 137.0 | P=0.6 |
| Perinatal mortality (per 1000) | 35.9 | 184.2 | P<0.05 |
| Fetal anomaly rate (%) | 1.5 | 13.2 | P<0.05 |
| Caesarean section rate (%) | 59.8 | 69.4 | P=0.3 |
| Neonatal hypoglycaemia rate (%) | 19.3 | 34.6 | P=0.06 |
| Macrosomia rate (%) | 18.7 | 25.6 | P=0.3 |
| Pre-eclampsia rate (%) | 1.9 | 7.9 | P<0.05 |
| Neonatal jaundice rate (%) | 11.7 | 23.1 | P=0.1 |
| Polycythaemia (%) | 0.74 | 7.7 | P<0.05 |
| Respiratory difficulties (%) | 19.3 | 23.1 | P=0.1 |
| Urinary tract infection (%) | 4.3 | 2.7 | P=0.6 |
| Hydramnios (%) | 3.1 | 0.0 | P=0.3 |
| Proteinuria (%) | 4.0 | 5.9 | P=0.6 |
| Ketonuria (%) | 0.0 | 0.6 | P=0.6 |

* n=23 for fetal outcomes



Pregnancy outcome: (table 3b): The untreated group had a 5 fold rate of PNM, 8 fold rate of fetal anomaly, 4 times rate of pre-eclampsia and a 10 times rate of polycythaemia compared with the treated group. The birth weights, rates of caesarean section, macrosomia and neonatal jaundice were comparable. There was a trend to higher rates of neonatal hypoglycaemia in untreated type 2 DM subjects compared with treated type 2 DM subjects.

### 4.1.4 Assessment of the impact of different forms of treatment in all the type 2 DM subjects.

Table 4a: Demographic indices of type 2 DM groups.

| | (OGLAs alone) N=99 | (OGLAs to Insulin) N=245 | (Diet/insulin) N=37 |
|---|---|---|---|
| Maternal age (years) | 34.5 ± 0.5† | 33.4 ± 0.3 | 31.4 ± 0.9 |
| Booking GA (weeks) | 21.6 ± 0.9 | 18.1 ± 0.5*† | 13.4 ± 1.4* |
| Parity (no) | 4.0 ± 0.2 | 3.9 ± 0.1 | 3.4 ± 0.3 |
| (BMI) ($kg/m^2$) | 32.5 ± 0.7 | 33.2 ± 0.4 | 31.1 ± 1.1 |
| Duration of diabetes (years) | 4.3 ± 0.5 | 4.5 ± 0.3 | 3.5 ± 0.8 |

* $P < 0.001$ vs OGLAs alone group

† $P < 0.05$ vs Diet/insulin

Demography (table 4a): The mean BMI, parity and duration of DM were similar in the type 2 diabetes groups. The OGLAs alone group were significantly older than the diet/insulin. The OGLAs alone group also booked later than other type 2 DM groups.

Table 4b: Proportions of untreated and trimester of booking of the type 2 DM groups.

| | (OGLAs alone) N=99 | (OGLAs to Insulin) N=245 | (Diet/insulin) N=37 |
|---|---|---|---|
| Proportion (%) of untreated | 32.4 | 2.4 | 13.5 |
| Proportions (%) booking in various Trimesters | | | |
| 1st Trimester | 32 | 40 | 67.6 |
| 2nd Trimester | 33 | 42.1 | 24.3 |
| 3rd Trimester | 35.2 | 17.9 | 8.1 |

While about a third of the OGLAs alone group were untreated, smaller percentage of diet/insulin group was not treated. Approximately equal proportions of the OGLAs alone treated subjects booked in all trimesters of pregnancy while the diet/insulin subjects booked mainly in the 1st trimester. The subjects who were converted from OGLAs to insulin booked predominantly in the 1st and 2nd trimesters of pregnancy.

Table 4c: Glycaemic profiles of type 2 DM groups.

| | (OGLAs alone) N=99 | (OGLAs to Insulin) N=245 | (Diet/insulin) N=37 |
|---|---|---|---|
| Booking HbA1c (%) | 7.1± 0.3 | 7.4 ± 0.1 | 7.9± 0.4 |
| Proportion (%) with booking HbA1c > 7% | 51.9 | 56.3 | 57.6 |
| 2nd Trimester Glycaemic levels | | | |
| HbA1c (%) | 6.7± 0.3 | 6.6± 0.2 | 6.3± 0.5 |
| FPG (mmol/l) | 5.3±0.2 | 6.1±0.1* | 5.9±0.3 |
| PPG (mmol/l) | 5.7±0.2 | 6.6±0.1* | 6.5±0.3 |
| 3rd Trimester Glycaemic levels | | | |
| HbA1c (%) | 6.2± 0.3 | 6.3± 0.1 | 5.5± 0.4 |
| FPG (mmol/l) | 5.2±0.1 | 5.5±0.1 | 5.4±0.2 |
| PPG (mmol/l) | 6.0±0.2 | 6.5±0.1† | 6.3±0.3 |
| Last HbA1c (%) | 6.5±0.2 | 6.4±0.1 | 6.6±0.3 |

HbA1c: Glycosylated haemoglobin, FPG: Fasting plasma glucose, PPG: Post prandial glucose, TM: Trimester.

* P < 0.001 vs group 1

† P < 0.05 vs group 1



Glycaemic profile (table 4c): Mean booking HbA1c levels were comparable at booking and higher than the desired goal of 7% in all groups. More than 50% of subjects in all groups had mean booking HbA1c > 7%. In all groups, mean HbA1c fell to target levels by the 2nd and 3rd trimesters. The FPG level though higher in the group converted from OGLAs to insulin compared with the OGLAs alone group in the 2nd trimester was similar in all groups in the 3rd trimester. However, the PPG level was higher in the group converted from OGLAs to insulin than the OGLAs alone group in the 2nd and 3rd trimesters.

Table 4d: Pregnancy outcomes of type 2 DM groups.

| | (OGLAs alone) N=99 | (OGLAs to Insulin) N=245 | (Diet/insulin) N=37 |
|---|---|---|---|
| Birth weight (grams) | 3185.2± 91.1 | 3259.0± 55.3 | 3238.8± 160.5 |
| PNM* (per 1000) | 125.0 | 28.0 | 33.0 |
| SB (per 1000) | 90.9 | 20.0 | 33.0 |
| NND (per 1000) | 34.1 | 8.0 | 0.0 |
| Fetal anomaly (%) | 5.7 | 2.0 | 0.0 |
| Caesarean section (%) | 62.5 | 59.8 | 58.1 |
| Neonatal hypoglycaemia (%) | 24.0 | 18.9 | 22.7 |
| Macrosomia (%) | 23.3 | 18.0 | 17.2 |
| Pre-eclampsia (%) | 3.5 | 2.1 | 0 |
| Neonatal jaundice rate (%) | 18.7 | 10.6 | 9.1 |
| Polycythaemia (%) | 2.7 | 1.0 | 0.0 |
| Urinary tract infection* (%) | 7.0 | 3.0 | 6.1 |
| Hydramnios (%) | 5.8 | 2.1 | 0.0 |
| Respiratory difficulties (%) | 20.0 | 19.9 | 13.6 |
| Proteinuria* (%) | 9.3 | 2.9 | 0.0 |
| Ketonuria (%) | 1.2 | 0.4 | 0.0 |

* $P < 0.05$; PNM: Perinatal mortality, SB: Still birth, NND: Neonatal death.

Pregnancy outcome (table 4d): There were higher than expected rates of PNM and proteinuria in the OGLAs alone treated group in comparison with other treatment groups while those converted from OGLAs to insulin had a lower than expected rate of urinary tract infection relative to the other groups.

Table 4e: Perinatal mortalities in type 1 DM subjects.

| No | Age (years) | Parity (no) | BMI (kg/m$^{2)}$ | Duration of DM (years) | Booking GA (weeks) | Delivery GA (weeks) | SB or NND | Booking HBA1C (%) | Last available HBA1C (%) | Associated Fetal Anomaly |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 36 | 3 | NA | NA | NA | 34 | SB | 10.4 | 5.4 | NO |
| 2 | 22 | 1 | NA | 10 | 23 | 24 | SB | NA | NA | NO |
| 3 | 28 | 2 | 32 | 16 | 8 | 37 | SB | 9.2 | 5.1 | NO |
| 4 | 30 | 3 | 52.9 | 1 | 37 | 37 | SB | 5.8 | 5.8 | YES |
| 5 | 22 | 2 | 33.8 | 16 | 18 | 38 | SB | 5.6 | 5.8 | NO |
| 6 | 21 | 1 | 28.1 | 4 | 32 | 32 | SB | NA | NA | NO |
| 7 | 27 | 3 | 28.3 | NA | 20 | 33 | SB | 6.3 | 8.2 | NO |
| 8 | 31 | 3 | NA | NA | 24 | 24 | SB | 7.4 | 7.4 | NO |
| 9 | 25 | 3 | 21.6 | 2 | 10 | 26 | NND | 8.1 | 4.9 | YES |
| 10 | 22 | 2 | 29.5 | 12 | 15 | 30 | NND | 6.2 | 7.0 | NO |
| 11 | 37 | 6 | 34.3 | 7 | 12 | 32 | NND | 10.7 | 9.3 | NO |
| 12 | 26 | 2 | 21.1 | 15 | 22 | 29 | SB | 7.6 | 5.6 | NO |
| 13 | 29 | 5 | 31.8 | NA | 9 | 37 | SB | 8.6 | 7.5 | NO |
| 14 | 27 | 5 | 27.1 | 8 | 30 | 33 | SB | 8.2 | 8.2 | NO |
| 15 | 25 | 4 | NA | 11 | 25 | 42 | SB | 12.3 | 12.3 | NO |
| 16 | 22 | NA | NA | 9 | 25 | 25 | SB | NA | NA | NO |
| 17 | 23 | 1 | 25 | 8 | 15 | 36 | SB | 5.9 | 9.0 | NO |

NA: not available

Table 4f: Perinatal mortalities in type 2 DM subjects.

| No | Treatment Modality | Age (years) | Parity (no) | BMI (kg/m$^{2)}$ | Duration of DM (years) | Booking GA (weeks) | Delivery GA (weeks) | SB or NND | Booking HBA1C (%) | Last available HBA1C (%) | Associated Fetal Anomaly |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | OGLAs | 40 | 4 | 23.6 | 3 | 11 | 27 | SB | 5.6 | 5.6 | NO |
| 2 | OGLAs | 36 | 5 | 30.3 | 5 | 8 | 38 | SB | 14.7 | 7.6 | NO |
| 3 | OGLAs | 32 | 4 | 30.6 | 3 | 28 | 36 | SB | 8.9 | 8.9 | NO |
| 4 | OGLAs | 31 | 3 | 29 | 3 | 23 | 35 | SB | 9.6 | 9.6 | NO |
| 5 | OGLAs | 36 | 5 | 33 | 6 | 21 | 35 | SB | 9.5 | 9.5 | NO |
| 6 | OGLAs | 35 | 4 | 36 | 3 | 23 | 27 | NND | NA | NA | NO |
| 7 | OGLAs | 34 | 3 | 53.5 | 7 | 18 | 24 | NND | 6.9 | 6.9 | YES |
| 8 | OGLAs | 43 | 3 | NA | 5 | 24 | 26 | NND | NA | NA | NO |
| 9 | OGLAs | 38 | 6 | 40.6 | 2 | 32 | 32 | SB | NA | NA | YES |
| 10 | OGLAs | 34 | 4 | 30.8 | 6 | 34 | 34 | SB | NA | NA | YES |
| 11 | OGLAs | 44 | 9 | 31.6 | 1 | 30 | 33 | SB | 8.7 | 8.7 | NO |
| 12 | OGLAs to Insulin | 31 | 6 | 29.3 | 2 | 33 | 37 | NND | 5.8 | 5.8 | NO |
| 13 | OGLAs to Insulin | 26 | 4 | 23.7 | NA | 18 | 31 | SB | 12.2 | 7.3 | NO |
| 14 | OGLAs to Insulin | 27 | 4 | NA | 3 | 17 | 34 | SB | 7.3 | 7.3 | NO |
| 15 | OGLAs to Insulin | 36 | 3 | 32.2 | 10 | 23 | 32 | NND | 7.8 | 7.8 | NO |
| 16 | OGLAs to Insulin | 32 | 4 | 36.4 | 3 | 9 | 25 | SB | 10.1 | 8.1 | YES |
| 17 | OGLAs to Insulin | 27 | 3 | 26.7 | NA | NA | 35 | SB | 6.2 | 5.3 | NO |
| 18 | OGLAs to Insulin | 33 | 3 | NA | 8 | 25 | 39 | SB | 10.2 | 10.2 | YES |
| 19 | Diet/insulin | 35 | 2 | 39.5 | 1 | 12 | 39 | SB | NA | NA | NO |

NA: not available

Table 4g. Profiles of perinatal mortalities in oral glucose lowering agents alone treated type 2 DM subjects.

| | 1st trimester treatment | 2nd trimester treatment | 3rd trimester treatment | Type of PNM | Booking GA (Weeks) | Delivery GA (Weeks) | Latest HbA1c (%) | Associated Fetal anomaly |
|---|---|---|---|---|---|---|---|---|
| 1 | Met 1350mg | Met 1700mg and Gli 10mg | Met 1700mg and Gli 10 mg | SB | 11 | 27 | 5.6 | Nil |
| 2 | Gli 20mg | Gli 10mg and Met 1700mg | Gli 5mg and Met 1700mg | SB | 8 | 38 | 7.6 | Nil |
| 3 | Gli 10mg | Gli 10mg | Gli 5mg and Met 1700mg | SB | 28 | 36 | 8.9 | Nil |
| 4 | Gli 5mg | Gli 5mg | Gli 10mg and Met 1700mg | SB | 23 | 35 | 9.6 | Nil |
| 5 | Gli 5mg | Gli 7.5mg and Met 1700mg | Gli 7.5mg and Met 1700mg | SB | 21 | 35 | 9.5 | Nil |
| 6 | Gli 15mg and Met 1000mg | Gli 15mg and Met 1000mg | Gli 15mg and Met 1000mg | NND | 23 | 27 | NA | Nil |
| 7 | Gli 20mg and Met 2000mg | Gli 20mg and Met 2000mg | | NND | 18 | 24 | 6.9 | Hydrocephalus+ |
| 8 | Gli 15mg | Gli 15mg | | NND | 24 | 26 | NA | Nil |
| 9 | Glicz 200mg | Glicz 200mg | Glicz 200mg | SB | 32 | 32 | NA | Phocomelia |
| 10 | Gli 20mg | Gli 20mg | Gli 10mg and Met 1700mg | SB | 34 | 34 | NA | Cranial deformities |
| 11 | Gli 2.5mg | Gli 2.5mg | Gli 2.5mg and Met 1700mg | SB | 30 | 33 | 8.7 | Nil |

Gli: Glibenclamide, Met: Metformin, Glicz: Gliclazide, PNM: perinatal mortality, SB: stillbirth, NND: neonatal death, NA: not available, GA: gestational age, HbA1c: haemoglobin A1c, +; treated for hypertension with ramipril before presentation.

Table 4h. Proportions (%) of various oral glucose lowering agents used by OGLAs alone treated type 2 DM subjects.

| Type of oral agent | 1st Trimester (N=99) | 2nd Trimester (N=83) | 3rd Trimester (N=79) |
|---|---|---|---|
| Glibenclamide | 41.1 | 34.9 | 19.0 |
| Gliclazide+ | 9.0 | 6.0 | 3.8 |
| Metformin | 21.2 | 23.0 | 20.3 |
| Glibenclamide and Metformin | 22.2 | 36.1 | 57 |
| Gliclazide+ and Metformin | 4.0 | 1.2 | 1.3 |
| Diet only | 2.0 | 0.0 | 0.0 |

+: Not included in therapy commenced at GSH

Table 4i: Profiles of type 1 DM pregnancies with fetal anomalies.

| Subject | Anomaly | Age (years) | Booking HBA1C | Comments |
|---|---|---|---|---|
| E.F | Achondroplasia | 36 | 8.9 | Booked at 12 weeks. |
| M.C | Bilateral multicystic kidneys | 25 | 8.1 | Booked at 10 weeks. |
| P.E | Incomplete descent of ceacum with hypoplastic aorta. | 30 | 5.8 | Booked at 37 weeks. |
| P.J | Pierre-Robin syndrome | 30 | 7.9 | Booked at 8 weeks. |
| J.D | Gastroschisis | 37 | 8.9 | Booked at 12 weeks. |

Table 4j: profiles of type 2 DM pregnancies with fetal anomalies.

| Subject | Anomaly | Age (Years) | Booking HBA1C (%) | Comments |
|---|---|---|---|---|
| Y.N | Phocomelia | 28 | - | Treated with glicazide before booking at 32 weeks. |
| G.C | Trisomy 13 | 27 | 7.8 | Treated with metformin before booking at 26 weeks. |
| F.K | Sacral agenesis, bifurcating ribs, renal hypoplasia. | 34 | 6.9 | Treated with gliclazide before booking at 25weeks |
| C.B | Cranial deformities and syndactyly | 34 | - | Treated with glibenclamide 20mg daily before booking at 34 weeks. |
| B.R | Ventricular Septal Defect, Pulmonary artery hypoplasia | 28 | 6.7 | Treated with gliclazide 80mg daily before booking at 26weeks |
| M.C | Anomalous pulmonary venous drainage, Stenosis of left pulmonary artery | 31 | 13.8 | Treated with metformin 1700g daily before booking at 10weeks. |
| M.K | Hydrocephalus and hydrancephaly | 34 | 6.9 | Treated with glibenclamide 20mg and metformin 2g daily before booking at 18 weeks of gestation. Patient was also on ramipril before booking. |
| K.R | Phocomelia | 32 | 10.1 | Treated with glibenclamide 15mg and metformin 2550mg before booking at the 9th week. She was also treated for hypertension enalapril before booking. |
| G.L | Phocomelia hydrocephalus, and retrognathia | 33 | 9.5 | Treated with glibenclamide 15mg daily before booking at 10weeks |
| V.R | Choanal atresia | 40 | 11.8 | Treated with glibenclamide 15mg daily before booking at 10weeks. |

There were 17 perinatal deaths in the type 1 diabetes group (table 4 e) of which 14 were stillbirths. Two of these perinatal deaths were associated with fetal anomalies. Nineteen perinatal deaths occurred in type 2 subjects (table 4f). This consisted of 11 in those treated with only OGLAs, 7 in those converted from OGLAs to insulin and one in the diet/insulin treated group. Eight of the 11 perinatal deaths in the OGLAs alone group and 5 of the 7 the group converted from OGLAs to insulin were stillbirths. All the perinatal deaths occurred in those treated with gliclazide, glibenclamide or a combination of glibenclamide and metformin (table 4g). There was no PNM in type 2 DM subjects who were treated with only metformin (table 4h).

The anomalies in the type 1 DM group (table 4i) included achondroplasia and Pierre-Robin syndrome, which are not diabetes related. Trisomy 13 was the only anomaly in the type 2 DM group not related to DM (table 4j). Three type 2 DM pregnancies were treated with gliclazide before booking while in another two pregnancies; hypertension was treated with enalapril in one and ramipril in another prior to presentation in our unit.

Chi square analysis demonstrated significant difference in the uncorrected PNM rates between the various groups with higher observed than expected rate in type 1 DM subjects and OGLAs alone type 2 DM group (type 1 DM patients were included in this analysis as they served as a "control" group for the assessment of the effect of OGLAs on PNM since they were all on insulin (n=197)). The diet/insulin treated type 2 DM group would have been a more ideal control group but had relatively small numbers of subjects (n=37). The uncorrected PNM rate per 1000 was 97 for the type 1 DM group and the rates in the type 2 DM groups are shown in table 4d.The PNM rates per 1000 corrected for untreated patients were: 67.1 in type 1 DM, 93.8 in OGLAs alone type 2 DM group, 24.8 in type 2 DM converted from OGLAs to insulin and zero in diet/insulin type 2 DM group ($p < 0.05$). Further correction for anomalies associated with PNM resulted in an additional decline in PNM rates per 1000 to 15.5 in type 1 DM and 16.7 in type 2 DM group converted from OGLAs to insulin, while that of OGLAs alone type 2 DM group, remained unchanged at 93.8 ($p < 0.05$). Logistic regression analysis was used to determine the variables that predicted PNM in our pre-gestational type 2 DM patients. Maternal age, BMI, ethnicity, parity, booking HbA1c, last recorded HbA1c, presence of fetal anomalies and treatment group were first explored in univariate models as independent variables; OGLAs and diet/insulin treated groups were entered into the model with the group converted from OGLAs to insulin as the reference group, (as it was the largest of the three type 2 DM groups). The factors predictive of PNM in univariate analysis were last HbA1c before delivery, use of OGLAs throughout pregnancy and the presence of fetal anomalies. These factors that were significant in univariate analysis were than entered into a multivariate model. The presence of fetal anomalies (Odds ratio (OR); 34.6; 95% confidence interval (CI) 2.7-444.5; p=0.006), treatment with OGLAs throughout pregnancy (OR 5.2; 95% CI, 1.4-18.8; p=0.01) and the last

HbA1c before delivery; (OR 1.7; 95% CI, 1.1-2.6; p=0.01) remained significantly predictive of PNM. The presence of fetal anomalies was however, no longer a significant predictor of PNM when untreated patients were excluded from the multivariate analysis.

Fetal anomaly rates did not differ between groups (table 4d). The fetal anomaly rate for all the pregnancies that were exposed to oral agents in the 1st trimester (calculated by combining the groups on OGLAs alone throughout pregnancy and those converted from OGLAs to insulin) was 3.1%. The rates corrected for untreated patients were 2.3% in type 1 DM, 1.6% group in OGLAs alone treated type 2 DM group and 1.7% in type 2 DM patients converted from OGLAs to insulin. Logistic regression analysis was done to determine the factors predictive of fetal anomaly in the cohort of types 1 and 2 DM subjects. The following factors were explored in univariate analysis: maternal age, BMI, booking HbA1c, 1st trimester HbA1c, gestational age at booking, duration of DM, lack of treatment and use of OGLAs in the first trimester. Treatment with OGLAs in the 1st trimester was entered by assessing all type 2 DM groups exposed to OGLAs in the first trimester against all type 1 and diet/insulin treated type 2 DM group. The type 1 DM and diet/insulin treated type 2 DM group were combined because of the small number of diet/insulin treated type 2 DM group (n=37). Maternal age (OR 1.0; 95% CI, 0.9-1.1; p=0.05), booking HbA1c (OR 1.3; 95% CI, 1.0-1.6; p=0.02), lack of treatment (OR 10.3; 95% CI, 3.5-29.8; p=0.00002) and 1st trimester HbA1c (OR 1.3; 95% CI, 1.0-1.7; p=0.02) were significant predictors in univariate model. When the factors that were significant in univariate models were explored in multivariate analysis, only lack of treatment remained significant (OR 46.5; 95% CI, 1.6-1320; p=0.02).

The birth weights, rates of macrosomia, caesarean section, respiratory difficulties, polycythaemia, neonatal hypoglycaemia, neonatal jaundice, pre-eclampsia, hydramnios and ketonuria were similar in all treatment groups.

We however further explored factors associated with macrosomia and hypoglycaemia in the cohort of pre-gestational types 1 and 2 DM using logistic regression analysis. Univariate analysis for macrosomia was first done using the following factors: maternal age, maternal height, BMI, weight gain in pregnancy, parity, gestational age at booking, lack of treatment, duration of DM, 2nd trimester HbA1c, 3rd trimester HbA1c, last HbA1c in pregnancy, 3rd trimester FPG, 3rd trimester PPG and ethnicity. Ethnicity in this analysis was limited to black Africans (n=185) and those of mixed ancestry (n=375). White women were excluded from this analysis due to their small number (n=37). Maternal height (OR 192.3; 95% CI, 5.2-7141.1; p=0.004), BMI (OR 1.1; 95% CI, 1.0-1.9; p=0.002) and parity (OR 1.1; 95% CI, 1.0-1.3; p=0.04) were predictive in univariate analysis. Maternal height (OR 153; 95% CI, 3.6-6465; p=0.008) and BMI (OR 1.1; 95% CI, 0.9-1.2; p=0.006) remained predictive of macrosomia in multivariate analysis using factors that were significant on univariate analysis.

Univariate logistic regression analysis for neonatal hypoglycaemia with 3rd trimester FPG, 3rd trimester PPG, last trimester HbA1c and treatment with OGLAs in the 3rd trimester as independent variables showed FPG and PPG in the 3rd trimester as independent predictors of hypoglycaemia (OR 1.2; 95% CI, 1.0-1.5; p=0.03 for FPG or PPG in the 3rd trimester). The use of OGLAs in the 3rd trimester was not associated with neonatal hypoglycaemia. Treatment with OGLAs in the 3rd trimester was assessed by comparing OGLAs alone treatment group against the combination of type 1 DM and type 2 DM groups treated with insulin in the 3rd trimester; i.e those converted from OGLAs to insulin and those in the diet/insulin group. When univariate logistic regression analysis with treatment with OGLAs in the 3rd trimester was done only in type 2 DM subjects, it was also found not to be predictive of neonatal hypoglycaemia.

## 4.2 Gestational Diabetes

There were 251 subjects with DM and 296 with IGT. The numbers of treated and untreated subjects are shown in table 5a. The majority of the DM and IGT groups were of mixed ancestral origin (84.9% and 84.5% respectively). There were 12 % of black Africans with DM while 14% had IGT. There were few white women in either group.

### 4.2.1 Treated DM versus treated IGT subjects

Demography: The DM subjects were older 33.2±0.4 vs 31.3±0.4 years, $p<0.05$ and of a higher parity; 3.7±0.1 vs 3.3±0.1; $p<0.05$ than the IGT subjects. Both groups were similarly obese with a mean BMI ($kg/m^2$) of 32.7±0.6 for DM vs 32.8±0.5 for IGT subjects. The booking gestational age of 25.2±0.4 for DM was similar to 26.3±0.4 weeks for IGT subjects.

Glycaemic control: The booking HbA1c (%) for DM of 5.0±0.1 vs 4.7±0.1 for IGT subjects, were comparable. The proportions of DM and IGT subjects with booking HbA1c > 6% were 26.5% and 17.5%, p=0.05 respectively. The 3rd trimester HbA1c (%) of 4.9±0.1 for the DM group was also similar to 4.7±0.1 in the IGT group. Although the mean 3rd trimester FPG (mmol/l) of 5.6±0.1 for the DM group was similar to 5.5±0.1 in the IGT, mean PPG (mmol/l) in the 3rd trimester was significantly higher in DM than IGT subjects; 6.3±0.1 vs 5.7±0.1, $p<0.05$.

Treatment in the 3rd trimester: The DM group was predominantly treated with insulin (64.6%) while the main form of therapy for IGT subjects was sole dietary therapy (51.8%). Diet alone was the form of therapy for 15.9% of DM subjects while insulin was the treatment modality for 26.6% of IGT subjects. Similar proportions of DM (19.5%) and IGT (21.6%) subjects were on OGLAs.

Table 5a: Pregnancy outcomes in GDM subjects.

| | DM | | IGT | |
|---|---|---|---|---|
| | Treated N=189 | Untreated DM N=62 | Treated N=215 | Untreated N=81 |
| Birth weight (grams) | 3078.6±48.4 | 3170.9±84.8 | 3141.1±45.2 | 3360.2±75.9 |
| PNM per 1000* | 16.1 | 86.2 | 4.8 | 0.0 |
| Fetal anomaly (%) | 2.5 | 0.0 | 0.7 | 2.3 |
| Macrosomia* (%) | 4.9 | 15.0 | 8.1 | 14.7 |
| Neonatal Hypoglycaemia (%) | 19.7 | 17.7 | 21.7 | 22.7 |
| Caesarean section (%) | 46.0 | 54.1 | 47.6 | 44.0 |
| Neonatal jaundice (%) | 11.1 | 20.6 | 13.3 | 7.7 |
| Polycythaemia (%) | 3.4 | 0.0 | 1.4 | 0.0 |
| Respiratory difficulties (%) | 5.1 | 11.8 | 3.5 | 2.3 |
| Urinary tract infection (%) | 6.4 | 1.6 | 4.8 | 2.7 |
| Hydramnios (%) | 0.5 | 3.3 | 0.0 | 1.4 |
| Proteinuria (%) | 3.2 | 6.5 | 1.4 | 1.4 |
| Ketonuria (%) | 0.5 | 0.0 | 0.0 | 1.4 |

*; $p < 0.05$ for treated vs untreated DM subjects.

Pregnancy outcome (5a): Despite the differences in age, parity, and PPG levels in the 3rd trimester, pregnancy outcomes (table 5a) were similar in the treated IGT and DM groups.

### 4.2.2 Treated versus untreated DM subjects

Demography: The treated and untreated DM subjects did not differ in age, parity or BMI; (33.2±0.4 vs 31.8±0.7 years, p=0.6), (3.7±0.1 vs 3.5±0.2, p=1.0) and (32.7±0.6 vs 33.5±1.0 kg/m$^2$ p=1.0) for age, parity and BMI of treated and untreated DM subjects respectively.

Glycaemic control: Booking HbA1c, 3$^{rd}$ trimester HbA1c and mean FPG in the 3$^{rd}$ trimester were similar in the 2 groups; (5.0±0.1 vs 5.3±0.3 %, p=0.6), (4.9±0.1 vs 5.1±0.3 %, p=1.0) and (5.6±0.1 vs 5.7±0.1 mmol/l p=1.0) for booking HbA1c, 3$^{rd}$ trimester HbA1c and 3$^{rd}$ trimester FPG levels of treated and untreated DM subjects respectively. The mean PPG levels in the 3$^{rd}$ trimester were comparable in treated; 6.2±0.1mmol/l and untreated subjects; 6.3±0.1 mmol/l, p=0.6. When treated and untreated subjects were combined, above target (>6.7mmol/l) 3$^{rd}$ trimester PPG were more common in the pregnancies with PNM than in those without (75% vs 25.6%, p < 0.05).

Treatment in the 3$^{rd}$ trimester: The majority of the treated subjects received insulin (64.6%) and similar proportions were on diet alone (15.9%) and OGLAs (19.5%). Equal proportions of the untreated patients were on diet alone (42.2%) and insulin (42.2%) and a fewer proportion were on OGLAs (15.6%).

Pregnancy outcome (5a): Macrosomia and PNM rates were significantly higher in the untreated diabetic subjects but the other pregnancy outcomes were similar.

### 4.2.3 Treated versus untreated IGT subjects

Demography: The treated and untreated IGT subjects were similar in age, parity and BMI; (31.3±0.4 vs 32.6±0.6 years, p=0.4), (3.3±0.1 vs 3.3±0.2, p=1.0) and (32.8±0.5 vs 33.4±0.8 kg/m$^2$ p=1.0) for age, parity and BMI of treated and untreated IGT subjects respectively. The untreated subjects, however, booked later than those who were treated (mean GA at booking of 35.3±0.6 vs 26.3±0.4 weeks, p<0.05).

Glycaemic control: All measures of glycaemic control at booking and in the 3$^{rd}$ trimester were similar in the 2 groups; (4.7±0.1 vs 4.6±0.1 %, p=1.0), (4.7±0.1 vs 4.6±0.1 %, p=1.0), (5.5±0.1 vs 5.4±0.1 mmol/l, p=1.0) and (5.7±0.1 vs 5.6±0.1 mmol/l, p=1.0) for booking HbA1c, 3$^{rd}$ trimester HbA1c, 3$^{rd}$ trimester FPG and 3$^{rd}$ trimester PPG of treated and untreated IGT subjects respectively.

Treatment in the 3$^{rd}$ trimester: 51.8% of treated subjects and 84.4% of untreated subjects were on diet alone. 26.6% of treated subjects and 11.1% of untreated subjects were on insulin. 21.6% of treated and 4.5% of untreated subjects received OGLAs,

Pregnancy outcome (5a): Despite the differences in booking GA, pregnancy outcomes were similar.

### 4.2.4 IGT subjects stratified by diagnostic FPG levels

The 2 strata of DFPG were: ≥5.5 and <5.5 mmol/l

Table 5b: Demographic and glycaemic variables of IGT subjects stratified by diagnostic FPG levels

| | < 5.5mmol/l N=140 | ≥5.5 N=156 | P value |
|---|---|---|---|
| Maternal age (years) | 31.4± 0.5 | 32.0± 0.5 | P = 0.3 |
| Booking GA (weeks) | 29.5± 0.6 | 28.0± 0.5 | P = 0.07 |
| Parity (no) | 3.2± 0.1 | 3.3± 0.1 | P = 0.5 |
| Booking BMI (kg/m$^2$) | 31.5± 0.7 | 34.2±0.7 | P = 0.02 |
| Booking HbA1c (%) | 4.8± 0.2 | 4.6±0.1 | P = 0.3 |
| Proportion with booking HbA1c > 6% | 19.1% | 14.9% | P = 0.4 |
| 3$^{rd}$ Trimester HbA1c (%) | 4.8± 0.2 | 4.6±0.2 | P = 0.3 |
| 3$^{rd}$ Trimester FPG (mmol/l) | 5.2± 0.1 | 5.7±0.1 | P <0.05 |
| 3$^{rd}$ Trimester PPG (mmol/l) | 5.4± 0.1 | 6.0±0.1 | P <0.05 |

Demography: Both groups were similar in age and parity. There was however, a tendency to significant differences in the gestational ages at booking. Subjects with DFPG ≥5.5 were more obese than those with DFPG < 5.5mmol/l.

Glycaemic control: The HbA1c levels at booking and in the 3$^{rd}$ trimester were similar in both strata of DFPG. The mean FPG (mmol/l) and PPG (mmol/l) in the 3$^{rd}$ trimester were higher in the ≥5.5 mmol/l than < 5.5 mmol/l group. Similar proportions of IGT subjects with DFPG > 5.5 mmol/l (19.1%) and DFPG ≥5.5 mmol/l (14.9%) had booking HbA1c levels > 6%, p=0.4.

Treatment in the 3$^{rd}$ trimester: 76% of those with DFPG ≥5.5 mmol/l and 44.3% of subjects with DFPG ≥5.5 mmol/l were treated with diet. The proportions (%) treated with insulin were: 9.6 of those with DFPG < 5.5 mmol/l and 34.3 of those with DFPG ≥5.5. The proportions of women with DFPG < 5.5 mmol/l and ≥5.5 mmol/l who were treated with OGLAs are 14.4% and 21.4% respectively.

Table 5c: Pregnancy outcomes in all IGT subjects stratified by diagnostic FPG values.

| | < 5.5mmol/l N=140 | ≥5.5 mmol/l N=156 | P value |
|---|---|---|---|
| Birth weight (grams) | 3198.4 ± 52.6 | 3193.0 ± 50.2 | P=0.9 |
| PNM per 1000 | 0.0 | 6.9 | P=0.3 |
| Fetal anomaly (%) | 2.1 | 0.0 | P=0.2 |
| Macrosomia (%) | 9.6 | 9.4 | P=1.0 |
| Neonatal hypoglycaemia (%) | 21.9 | 22.0 | P=1.0 |
| Caesarean section (%) | 44.1 | 49.0 | P=0.4 |
| Neonatal jaundice (%) | 8.5 | 6.6 | P=0.6 |
| Polycythaemia (%) | 1.1 | 1.1 | P=1.0 |
| Respiratory difficulties (%) | 1.1 | 5.5 | P=0.09 |
| Urinary tract infection (%) | 3.0 | 5.4 | P=0.3 |
| Hydramnios (%) | 0.7 | 0.0 | P=0.3 |
| Proteinuria (%) | 0.0 | 2.7 | P=0.06 |
| Ketonuria (%) | 0.0 | 0.7 | P=0.3 |

Pregnancy outcome: The pregnancy outcomes were similar in both DFPG strata (table 5c) in spite of the differences in BMI and glycaemia in the 3rd trimester, although there was a tendency towards increased rates of respiratory difficulties and proteinuria in subjects with DFPG ≥5.5 mmol/.

### 4.2.5 Examination of outcomes solely in relation to 2hour OGTT plasma glucose EASD criteria for gestational glucose intolerance

The IGT subjects were stratified using the 2hour OGTT plasma glucose levels into < 9.0 mm0l/l and ≥ 9.0 < 11.0-mmol/l.

Table 5d: Demographic and glycaemic variables of IGT subjects stratified by EASD 2hour OGTT plasma glucose values.

| | < 9mmol/l N=110 | ≥ 9.0mmol/l N=186 | P value |
|---|---|---|---|
| Maternal age (years) | 31.3± 0.5 | 31.9± 0.4 | P = 0.3 |
| Booking GA (weeks) | 29.1± 0.7 | 28.4± 0.5 | P = 0.4 |
| Parity (no) | 3.4± 0.2 | 3.2± 0.1 | P = 0.3 |
| Booking BMI (kg/m$^2$) | 32.9± 0.8 | 33.0±0.6 | P = 0.9 |
| Booking HbA1c (%) | 4.8± 0.2 | 4.6±0.1 | P = 0.3 |
| Proportion with booking HbA1c > 6% | 17.2% | 16.5% | P = 0.9 |
| 3$^{rd}$ Trimester HbA1c (%) | 4.5± 0.2 | 4.8±0.1 | P = 0.2 |
| 3$^{rd}$ Trimester FPG (mmol/l) | 5.4± 0.1 | 5.4±0.1 | P =1.0 |
| 3$^{rd}$ Trimester PPG (mmol/l) | 5.7± 0.1 | 5.7±0.1 | P =0.6 |

Demography (table 5d): There were no differences in the maternal ages, BMI, parity, and booking GA between groups.

Glycaemic control (table 5d): All assessed indices of glycaemic control (booking HbA1c, HbA1c in the 3$^{rd}$ trimester, FPG in the 3$^{rd}$ trimester, PPG in the 3$^{rd}$ trimester, proportions of subjects with booking HbA1c levels > 6%) were similar.

Treatment in the 3$^{rd}$ trimester: 65.9% of subjects with 2hour OGTT plasma glucose < 9 mmol/l and 53.2% with 2hour OGTT plasma glucose > 9 mmol/l were solely treated with diet. OGLAs was the treatment modality for 18.2% of those with 2hour OGTT plasma glucose < 9 mmol/l compared with 18.6% of those in the second group. Insulin therapy was used by 15.9% of those with 2hour OGTT plasma glucose < 9 mmol/l and 28.2% of subjects with 2hour OGTT plasma glucose > 9 mmol/l.

Table 5e: Pregnancy outcomes in all IGT subjects stratified by EASD 2hour OGTT plasma glucose values.

| | < 9mmol/l N=110 | ≥ 9.0mmol/l N=186 | P value |
|---|---|---|---|
| Birth weight (grams) | 3233.3 ± 59.6 | 3178.1 ± 45.7 | P=0.5 |
| PNM per 1000 | 0.0 | 6.0 | P=0.4 |
| Fetal anomaly (%) | 0.0 | 1.7 | P=0.3 |
| Macrosomia (%) | 11.3 | 8.9 | P=0.5 |
| Neonatal hypoglycaemia (%) | 19.4 | 23.3 | P=0.5 |
| Caesarean section (%) | 53.8 | 42.5 | P=0.06 |
| Neonatal jaundice (%) | 6.1 | 8.4 | P=0.6 |
| Polycythaemia (%) | 1.5 | 0.8 | P=0.7 |
| Respiratory difficulties (%) | 4.6 | 2.5 | P=0.5 |
| Urinary tract infection (%) | 3.8 | 4.5 | P=0.8 |
| Hydramnios (%) | 0.0 | 0.6 | P=0.4 |
| Proteinuria (%) | 0.0 | 2.2 | P=0.1 |
| Ketonuria (%) | 0.0 | 0.6 | P=0.4 |

Pregnancy outcome (table 5e): Pregnancy outcomes were similar in both strata of IGT subjects. There was however, a trend towards a significantly increased caesarean section rate in the group with 2hour OGTT plasma glucose value < 9mmol/l.

### 4.2.6 The effect of treatment modality on outcomes in GDM subjects

The study population (GDM and GIGT) was categorized based on treatment modality into the following 4 groups, 1; diet alone, 2; OGLAs, 3; converted from OGLAs to insulin, 4; insulin. Patients receiving less than 4 weeks of treatment (untreated) were excluded from this analysis.

Table 5f: Demographic and glycaemic variables of treated GDM subjects

| | Group 1 Diet only N=150 | Group 2 OGLAs N=78 | Group 3 OGLAs to insulin N=38 | Group 4 Insulin N=139 |
|---|---|---|---|---|
| Maternal age (years) | 31.3±0.4 | 33.0±0.6 | 32.2±0.9 | 32.6±0.5 |
| BMI (kg/m$^2$) | 31.2±0.6 | 33.6±0.9 | 34.6±1.2 | 33.4±0.6 |
| Parity (no) | 3.1±0.1 | 3.6±0.2 | 3.8±0.3 | 3.7±0.1* |
| Booking GA (weeks) | 27.9±0.4†‡§ | 24.8±0.6*‡ | 20.1±0.9*†§ | 25.5±0.5*‡ |
| Booking HbA1c (%) | 4.8±0.2 | 4.7±0.2 | 4.5±0.2 | 5.1±0.1 |
| Proportion (%) with Booking HbA1c >6% | 26.1 | 18.3 | 8.3 | 26.4 |
| 3rd Trimester HbA1c (%) | 5.0±0.2 | 4.6±0.2 | 4.6±0.3 | 5.0±0.1 |
| 3rd Trimester FPG (mmol/l) | 5.3±0.1 | 5.3±0.1 | 5.9±0.1*† | 5.7±0.1*† |
| 3rd Trimester PPG (mmol/l) | 5.4±0.1 | 5.9±0.1* | 6.6±0.1*† | 6.4±0.1*† |

GA; gestational age, TM; trimester, FPG; fasting plasma glucose, PPG; post prandial glucose

* $p < 0.05$ vs group 1
† $p < 0.05$ vs group 2
‡ $p < 0.05$ vs group 3
§ $p < 0.05$ vs group 4

Demography (table 5f): The mean ages and BMI were similar in all groups. There were significant differences in the booking gestational ages between all groups except groups 2 and 4.

Glycaemic control (table 5f): The booking and 3rd trimester HbA1c levels were comparable in all groups. The 3rd trimester FPG and PPG levels were significantly higher in groups 3 and 4 than in groups 1 and 2. Group 3 subjects showed a lower than expected proportion of subjects with booking HbA1c > 6%, nearly reaching significance p=0.08 on chi square analysis.

Table 5g: Pregnancy outcomes of treated GDM subjects.

| | Group 1 Diet only N=150 | Group 2 OGLAs N=78 | Group 3 OGLAs to insulin N=38 | Group 4 Insulin N=139 |
|---|---|---|---|---|
| Birth weight (grams) | 3104.2± 54.6 | 3109.6 ± 74.5 | 3122.5 ± 106.7 | 3123.6 ± 55.8 |
| PNM per 1000¶ | 0.0 | 0.0 | 52.6 | 14.4 |
| Fetal anomaly (%) | 1.0 | 1.9 | 3.5 | 1.1 |
| Macrosomia¶ (%) | 7.6 | 9.0 | 2.6 | 5.0 |
| Neonatal hypoglycaemia (%) | 22.7 | 18.9 | 7.1 | 24.4 |
| Caesarean section¶ (%) | 43.8 | 51.3 | 23.7 | 54.6 |
| Neonatal jaundice (%) | 8.3 | 11.3 | 3.6 | 11.6 |
| Polycythaemia (%) | 1.0 | 0.0 | 7.1 | 3.5 |
| Respiratory difficulties (%) | 3.1 | 1.9 | 3.6 | 6.9 |
| Pre-eclampsia (%) | 2.1 | 0.0 | 0.0 | 2.0 |
| Urinary tract infection (%) | 2.7 | 6.4 | 10.5 | 7.1 |
| Hydramnios (%) | 0.0 | 0.0 | 0.0 | 0.7 |
| Proteinuria (%) | 1.4 | 3.9 | 0.0 | 0.7 |
| Ketonuria (%) | 0.0 | 0.0 | 0.0 | 0.7 |

GA; gestational age, TM; trimester, FPG; fasting plasma glucose, PPG; post prandial glucose

¶ $p < 0.05$ for chi square

The group that was converted from OGLAs to insulin showed a higher than expected rate of PNM but lower than expected rates of caesarean section and macrosomia.

Table 5h: Perinatal mortalities in GDM subjects.

| No | Type GDM DM/IGT | Age (years) | Parity (no) | BMI ($kg/m^{2)}$ | Booking GA (weeks) | Delivery GA (weeks) | SB or NND | Booking HBA1C (%) | Last available HBA1C (%) | Associated Fetal Anomaly |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | DM | 36 | 3 | 24.8 | 16 | 30 | SB | 2.8 | 2.8 | NO |
| 2 | DM | 36 | 6 | NA | 35 | 36 | SB | NA | NA | NO |
| 3 | DM | 36 | 6 | NA | 12 | 36 | SB | NA | NA | NO |
| 4 | DM | 30 | 5 | 24.7 | 27 | 29 | NND | 3.9 | 3.9 | NO |
| 5 | DM | 19 | 1 | 30 | 14 | 31 | NND | 7.3 | 7.3 | NO |
| 6 | DM | 31 | 3 | 31.6 | 15 | 36 | SB | 5.5 | 6.5 | NO |
| 7 | DM | 31 | 4 | 32.9 | 34 | 34 | SB | NA | NA | NO |
| 8 | DM | 33 | 4 | 38.1 | 10 | 27 | SB | 3.7 | 3.7 | NO |
| 9 | IGT | 25 | 1 | 22.6 | 16 | 37 | SB | 6.2 | 6.2 | NO |

Table 5i: profile of GDM pregnancies with fetal anomalies

| Subject | Treatment Type | Anomaly | Age (years) | Booking HBA1C (%) | Comments |
|---|---|---|---|---|---|
| A.M | IGT | Oesophageal atresia | 34 | 3.3 | Patient booked at 17 weeks, live birth at 38 weeks. |
| N.N | IGT | Spina bifida with meningomyelocele | 37 | NA | Booked at 36 weeks and delivered at 40 weeks. |
| S.N | DM | Hydrocephalus | 23 | 6.0 | Patient booked at 16 weeks with live birth at 38 weeks |
| L.D | DM | Left multicystic kidney | 31 | 6.0 | Patient booked at 16 weeks with live birth at 34 weeks |
| B.S | DM | Hydrocephalus | 30 | 5.4 | Booked at 16 weeks with termination of pregnancy at 17 weeks due to fetal anomaly |



Pregnancy outcome in GDM subjects by treatment groups: There were 9 perinatal deaths in the cohort of GDM subjects (table 5h). Eight occurred in DM subjects; consisting of 6 stillbirths and 2 neonatal deaths. The lone fetal death in the IGT group was a stillbirth. There were no fetal anomalies associated with the perinatal deaths in either the DM or IGT group.

Chi square test showed significant difference in the rates of PNM (table 5g). There was no PNM in those patients treated with diet only (n=150) or OGLAs alone (n=78), but group 3 (OGLAs to insulin) had a greater than expected rate of PNM. Logistic regression analysis was conducted in the cohort of GDM subjects (DM + IGT) to determine factors predictive of PNM. We first explored the following variables in univariate models: age, BMI, booking GA, parity, ethnicity, booking HbA1c, 3rd trimester HbA1c, last HbA1c, 3rd trimester FPG and

3rd trimester PPG. The treatment groups 1,2,3 were also individually explored with group 4 as control. The 3rd trimester PPG; (OR 2.3, CI: 1.1-4.6, $p < 0.05$), FPG at diagnosis; (OR 1.4, CI: 1.1-1.8, $p < 0.05$) and 2hour OGTT plasma glucose value; (OR 1.2, CI: 1.0-1.5, $p < 0.05$) were significant predictors of PNM in the univariate analysis. In multivariate analysis with 3rd trimester PPG, diagnostic FPG and 2hour OGTT plasma glucose value as independent variables, only 3rd trimester PPG remained significantly predictive of PNM (OR 2.1, CI: 1.0-4.5; $p < 0.05$).

The rates of macrosomia and caesarean section were lower than expected in those converted from OGLAs to insulin in comparison with other GDM treatment groups (table 5g). The following factors were explored in univariate models to determine their association with macrosomia: maternal age, height, BMI, parity, booking gestational age, lack of treatment, 2nd trimester HbA1c, 3rd trimester HbA1c, last HbA1c before delivery, DFPG, 2hour OGTT plasma glucose value, 3rd trimester FPG, 3rd trimester PPG, weight gain in pregnancy and ethnicity. White women were were excluded from the analysis on ethnicity because of the small numbers. The factors that were significant in univariate models are; maternal height (OR 775, CI: 7.8-77216, $p < 0.05$), BMI (OR 1.1, CI: 1.0-1.1, $p < 0.05$), parity (OR 1.2, CI: 1.0-1.4, $p < 0.05$), booking gestational age (OR 1.1, CI: 1.1-1.2, $p < 0.05$), lack of treatment (OR 1.5, CI: 1.2-2.0, $p < 0.05$) and being black African (OR 4.2, CI: 2.1-8.4, $p < 0.05$). No glycaemic index was predictive of macrosomia in our cohort of gestational DM. In multivariate analysis using factors that were significant on univariate analysis, only being black African remained significantly predictive of macrosomia (OR 6.2, CI: 1.5-25.6, $p < 0.05$).

The rates of fetal anomaly, neonatal hypoglycaemia, neonatal jaundice, respiratory difficulties, polycythaemia, pre-eclampsia, hydramnios, urinary tract infection, proteinuria and ketonuria were comparable across all GDM treatment groups (table 5g).

None of the following factors: maternal age, BMI, booking HbA1c, lack of treatment, booking gestational age and treatment group was predictive of fetal anomaly in the cohort of GDM subjects on univariate analysis nor were the 3rd trimester glycaemic indices (FPG, PPG, last HbA1c before delivery) and treatment modality predictive of neonatal hypoglycaemia.

# CHAPTER 5: DISCUSSION

## 5.1 Pre-gestational diabetes

As might be anticipated from the earlier onset of diabetes in type 1 DM and in keeping with other studies (21,29,32), the treated type 1 DM patients were younger, of lower parity and had a longer duration of DM than the treated type 2 DM group. The earlier gestational age at booking by treated type 1 DM and insulin treated type 2 DM subjects when compared with other type 2 DM treatment groups was notable. This may be partly explained by the former two groups being more likely to have been under closer medical observation because of their treatment with insulin. The younger age of insulin only treated type 2 DM subjects in comparison with those treated with only oral hypoglycemic agents suggests that they might include those with type 1 DM who may have been misclassified as type 2 DM.

A poor level of glycaemic control at booking in the treated types 1 and 2 DM subjects is unacceptable as it is a significant predictor of adverse pregnancy outcomes (21). So too is the observation of the later booking of the type 2 DM group as this implies that they were exposed to a longer period of hyperglycaemia before the benefit of supervised treatment in GSH than the type 1 DM group. These findings are a reflection of inadequate pre-pregnancy care in the community, which is not surprising as there is evidence that diabetes care in Cape Town primary care clinics is suboptimal (142). Supervised care at a tertiary care facility (GSH) with a maternity unit dedicated to the management of diabetes in pregnancy resulted in the attainment of target HbA1c goals by the $2^{nd}$ and $3^{rd}$ trimesters in treated types 1 and 2 DM subjects. This demonstrates that good glycaemic control is possible in these patients. Conception should only be encouraged in diabetic women when target glycaemic levels have been met and the patient fully understands the implication of pregnancy with DM.

The discrepancy between glycaemic profile assessed as HbA1c or FPG and PPG during gestation indicates that these measures of blood glucose control are complimentary rather than substitutes for assessing glycaemia. Fasting plasma glucose and PPG assess immediate and short-term blood glucose control and better reflect the daily fluctuations in glycaemic control while HbA1c allows for a review of mean glycaemic control over the previous 2-3 months.

The PNM rate was high in both groups of untreated pre-gestational DM, particularly so in the type 1 group. As the PNM data in the latter group was only available in 12 of the 21 patients, the reported rate may well be an overestimate of the true rate. However, even if there were no perinatal deaths in the remaining 9 cases, the PNM would still be extremely high. This clearly highlights the very high risk of untreated pre-gestational diabetes and underscores the all-important need for early referral to a dedicated center charged with diabetic

management in pregnancy. Indeed it is apparent that the present framework in which women with diabetes are presently managed needs reassessment. One suggestion is that all diabetic women in the reproductive age group should be advised to have effective contraception until pregnancy is desired. Perhaps this will allow for proper pre pregnancy care before conception.

The PNM rates for the treated type 1 DM subjects were comparable to that previously reported from our center (11) when the overall PNM rate was 77 per 1000 and to 66 per 1000 obtained from a study in France (143). They are however, higher than those reported in several other studies; 17 per 1000 (21), 12.5 per 1000 (14), 28 per 1000 (144), 31 per 1000 (145) and 38 per 1000 (146). Correction for fetal anomalies in our treated type 1 DM patients reduced the PNM rate from 67 per 1000 to 15.5 per 1000 emphasizing the significance of fetal anomalies as a cause of perinatal deaths in our setting. Similar to other studies (143-145,147), poor glycaemic control was associated with PNM.

Treated type 2 DM subjects in common with treated type 1 DM subjects had a PNM rate that was lower than untreated type 2 DM counterparts; 35.9 per 1000 versus 184.2 per 1000, $p < 0.05$, again illustrating the significance of adequate therapy for glycaemia in reducing PNM. Analysis of the 19 perinatal deaths in type 2 DM subjects showed that 11 occurred in those treated with OGLAs alone while 7 occurred in those converted from OGLAs to insulin. Only one occurred in the non-OGLAs exposed group. These findings tend to suggest that OGLAs were deleterious with respect to PNM. This was supported by the logistic regression analysis, which confirmed the sole use of OGLAs, poor glycaemic control and the presence of fetal anomalies as independent risk factors for PNM. Interestingly, the conversion soon after booking from OGLAs to insulin in type 2 DM subjects was not independently associated with PNM, suggesting events related to the use of OGLAs later in pregnancy to be causative of PNM. Furthermore, no PNM occurred in pregnancies treated with metformin in the 2$^{nd}$ and 3$^{rd}$ trimesters of pregnancy. Perinatal deaths were confined to type 2 DM pregnancies in which hyperglycaemia was treated with gliclazide, glibenclamide or a combination of glibenclamide and metformin. The mechanism whereby glibenclamide or gliclazide alone or in combination with metformin contributes to PNM is not clear and requires further study. The PNM rates for our treated and untreated DM subjects though lower than 70 per 1000 and 313 per 1000 for treated and untreated type 2 DM subjects respectively in an earlier study from our center (3) also showed lower PNM in those switched from combined OGLAs to insulin in comparison with those treated with OGLAs alone. The PNM rate for our cohort of treated type 2 DM subjects was not different from that reported by Huddle (28 per 1000) (146) and Cundy et al (46.1 per 1000) (29). Clausen et al (21) however, found a higher PNM rate (67 per 1000).

Our finding of a higher PNM in type 1 compared with type 2 DM patients is similar to that of Huddle (146). It is of interest, considering that demographic variables associated with adverse PNM such as parity and BMI albeit at booking were higher in our type 2 DM compared with the type 1 DM subjects. The latter group tended to have poorer measures of glycaemic control such as higher booking HBA1C levels (p=0.06), 2nd trimester FPG and 3rd trimester PPG which may partly account for the differences in rates of PNM. In contrast, Clausen et al (21) observed a higher PNM in type 2 DM compared with type 1 DM subjects despite better glycaemic profiles in type 2 DM patients. Cundy et al (29) also found a higher PNM rate in their cohort of type 2 DM compared with the type 1 patients. No reasons were proffered in these studies to explain these findings. The type 2 DM patients in these latter studies, like our patients were significantly older, more obese and booked later and had a shorter duration of DM than the type 1 DM subjects.

The fetal anomalies described in our patients are consistent with that described in other studies (21, 29-31) with skeletal, cardiovascular and nervous system anomalies as the dominant abnormalities. The undisputable value of treatment in reducing the occurrence of fetal anomalies is reflected by the 10 fold higher rate of fetal anomalies in untreated type 1 and type 2 DM subjects compared with treated types 1 and 2 DM subjects and logistic regression analysis failed to reveal the use of OGLAs in early pregnancy as predictive of fetal anomalies in the latter groups, whilst lack of treatment was predictive in multivariate analysis. These findings argue against glibenclamide and metformin being teratogenic. It is pertinent to note that other studies in which pregnant type 2 DM subjects had routinely been converted from OGLAs to insulin at booking (21, 146) also reported comparable rates of fetal anomalies to that in their type 1 DM patients. This is despite the fact that these pregnancies were largely unplanned and patients often booked after the first trimester. Although not stated, these patients were presumably still receiving pre-pregnancy treatment prior to booking, which more often than not would have been OGLAs. The finding of a significant association between lack of treatment and fetal anomalies will suggest that lack of treatment per se or the presence of factors associated with lack of treatment as contributory to the occurrence of fetal anomalies. Possible aetiologic factors in the fetal anomalies seen in our DM subjects include continued use of glibenclamide in high doses, exposure to gliclazide and not discontinuing teratogenic anti-hypetertensives like ramipril and enalapril by untreated patients. The important need for adequate treatment is also shown by the vital link between fetal anomalies and PNM in that fetal anomalies ceased to be predictive of PNM once untreated patients were excluded.

The comparable rates of neonatal hypoglycaemia in infants of treated types 1 and 2 DM subjects are noteworthy. One may however, argue that as 74% of type 2 DM subjects were already on insulin in the third trimester, these data are not surprising. It is significant that the rates of neonatal hypoglycaemia did not

differ amongst type 2 DM subjects treated by various modalities nor did it differ when type 2 DM patients treated with insulin in the 3rd trimester (n=282) were compared with type 2 DM subjects who were on OGLAs alone in the 3rd trimester (n=99). Furthermore, logistic regression analysis did not reveal the use of OGLAs in the 3rd trimester as significantly predictive of neonatal hypoglycaemia. These observations may be a result of the practice by the unit of not exceeding 10 mg of glibenclamide and replacing OGLAs with continuous intravenous insulin infusion during delivery.

It was expected that the higher mean birth weights and rates of macrosomia in type 2 DM compared with type 1 DM pregnancies would be explained by older maternal age, higher BMI and greater parity, factors that have been reported to be associated with macrosomia. However, logistic regression analysis found maternal height and BMI to be significant in multivariate analysis. A significant association between maternal height and fetal macrosomia has been reported by some (148) but not other investigators (37).

The high rate of caesarean section in our treated type 1 and 2 DM patients is probably a reflection of the preference for repeat caesarean section over trial of scar by the unit as previous caesarean section was the commonest indication for caesarean section.

The more than 2 fold higher rate of UTI in treated type 1 compared with type 2 DM subjects may be related to the poorer glycaemic control in the former. Their higher proteinuria rate with a tendency to significance may partly be explained by the higher UTI rate and a possible higher rate of nephropathy given the longer duration of DM and poorer glycaemic control in treated type 1 compared with type 2 DM subjects. It is not surprising that the neonatal jaundice rate for untreated type 1 DM was 3.6 times that of treated type 1 DM subjects nor is the finding that untreated type 2 DM patients had a 4 times higher rate of pre-eclampsia and 11 times higher rate of polycythaemia than treated type 2 DM subjects as these are frequent consequences of inadequate treatment.

## 5.2 Gestational Diabetes

The older age, higher parity and earlier booking in the GDM subjects classified as DM than IGT subjects are expected as these factors positively correlate with the severity of glucose intolerance.

That GDM indeed represents a less severe degree of glucose intolerance compared with pre-gestational diabetes is indicated by the fact that mean HBA1C levels at booking and throughout pregnancy were less than 6% for the GDM subgroups compared with over 7% for types 1 and 2 DM subjects. It is also pertinent to note that similar to that observed in our pre-gestational types 1 and

2 DM, the HbA1c levels were comparable between the IGT and DM subgroups of GDM while FPG and PPG levels often differed.

There was a clear benefit of even 4 weeks of treatment in the GDM subjects who fell into the DM category. This subgroup not only had a PNM rate that was significantly lower than untreated frank DM subjects, but also lower than the overall PNM rate of 30 per 1000 for the PMNS. This might be a reflection of the superior obstetric care provided at the maternity unit of GSH compared with the other facilities in the PMNS.

In contrast, the same cannot be said about the subjects with IGT in whom treatment made no difference to the PNM, though treated and untreated IGT subjects had low rates of PNM. These findings are similar to that of the ACHOIS trial (7) in which the PNM rates of routinely versus intensively treated IGT subjects failed to reach significance. This Australian study, which is the first randomized study to examine the benefits of treating IGT however, showed a significant reduction in a composite primary outcome that included perinatal death and macrosomia related morbidities namely: shoulder dystocia, bone fracture and nerve palsy in intensively versus routinely treated IGT subjects defined with the 1985 WHO study group criteria as in our study. Three other studies, from China (137), United Kingdom (138) and Mauritius (139) have reported rates of PNM for treated IGT similar to glucose tolerant women. The Chinese study, similar to that from Australia showed a significantly increased risk of macrosomia, breech presentation, premature rupture of the membranes and preterm birth. The Mauritian study reported a PNM rate of 22 per 1000 for treated IGT subjects similar to 26 per 1000 for their background population in contrast to the much higher PNM rates of 116 and 124 per 1000 for DM and pre-gestational diabetes. The Mauritian group (139) concluded that while women with frank diabetes diagnosed in pregnancy had the same risks as pregnant women with pre-gestational diabetes, they did not support the use of limited resources to identify and manage IGT in pregnancy in the same manner as those with frank diabetes.

Our findings also, question the wisdom of intensive treatment for gestational IGT in developing countries as "untreated" IGT in our cohort had an excellent PNM. It is however; pertinent to bear in mind that "untreated" in this study is defined as receiving less than 4 weeks of supervised care. Perhaps, even less than 4 weeks of supervised care is adequate to provide significant benefits in terms of PNM for pregnancies with mild degrees of glucose tolerance. Additional factors may account for the excellent PNM rates in our IGT subjects and the absence of the macrosomia related adverse morbidities, which occurred, in the Australian and Chinese studies. These include the routine practice of induction of labor at $38^{th}$ week of gestation and the practice of offering caesarean section to our patients with macrosomic babies with abdominal circumference > $90^{th}$ percentile even in

"untreated" patients. This may indeed suggest that simple obstetric measures in IGT subjects may considerably reduce PNM rates.

The PNM rates observed in this study are in agreement with the rate of 10 per 1000 previously reported from our centre (9) despite the earlier subjects not being subdivided into DM and IGT. In contrast, Huddle from Soweto Johannesburg (146) reported a PNM rate of 42 per 1000 for gestational diabetes. These differences may be accounted for by the lack of distinction between DM and IGT and the possibility that a number of subjects had undiagnosed pre-gestational diabetes. This is suggested by the high mean booking HbA1c of 7.1% in their study.

Although one might have expected fetal outcomes to differ in subjects when stratified by diagnostic FPG as high FPG levels are indicative of more severe disease, this was not so. There was however, a trend towards significantly higher rates of respiratory difficulties ($p=0.09$) and proteinuria ($p=0.06$) in the DFPG $\geq$ 5.5 mmol/l than the $<$ 5.5 mmol/l group. These comparable findings irrespective of the DFPG group are unlikely to be explained by lack of fasting as the diagnosis of GDM was made after 2 OGTTs. Perhaps excess PNM related to glucose intolerance per se is only seen at DFPG levels in the diabetic range as suggested by the finding that only one of 43 women with perinatal deaths in the Mauritius study (139) had fasting hyperglycaemia below 7.8 mmol/l at presentation.

The similar perinatal mortality and morbidity rates in IGT subjects by 2hour OGTT plasma glucose $\geq$ 9mmol/l and $<$ 9 mmol/l is of interest as it argues against any advantage in using the EASD criteria over the WHO 2hour OGTT plasma glucose threshold for GDM. The rate of caesarean section however, showed a surprising trend towards significant increase in the $\geq$ 9mmol/l compared with the $<$ 9mmol/l group. Our findings are similar to those of Lao et al (149) who reported no difference in perinatal outcomes of GDM subjects diagnosed by the 1980 WHO criteria regardless of a 2-hour post OGTT plasma glucose $\geq$ 8.0 mmol/l - $<$ 9mmol/l or $\geq$ 9mmol/l - $<$ 11mmol/l. The comparable perinatal mortality and morbidity rates we found however require confirmation in larger studies.

Stratification of our IGT subjects by FPG and 2hour OGTT plasma glucose levels did not identify any subgroup with worse pregnancy outcomes but in Cape Town, GDM is diagnosed based on selective screening. It is highly likely that universal screening as has been recommended following the results of the ACHOIS trial, will uncover more cases of GDM (110,119). However, if universal screening is not affordable as in our setting we are reassured that GIGT in our centre with even minimal intervention (less than 4 weeks of supervised care) has a good outcome as most of those cases missed in selective screening belong to the GIGT group (110). Costs may be saved without increasing PNM by treating IGT subjects less intensively than DM subjects in our centre.

In the analysis of PNM in pre-gestational type 2 DM patients, the last HbA1c before delivery and use of OGLAs throughout pregnancy were independently predictive of PNM. In this study however, in the GDM subjects, the form of therapy for hyperglycaemia was not independently associated with PNM. There was no mortality in the cohort of 78 GDM subjects treated with OGLAs alone, most of who were treated with a combination of metformin and glibenclamide. These findings support the randomized controlled trial of Langer et al (76) that glibenclamide exposure in late pregnancy in GDM is not deleterious. The present study showed poor glycaemic control in GDM subjects measured as PPG in the 3rd trimester as a predictor of PNM and highlights the limitation in using HbA1c as a measure of blood glucose control in GDM. The majority of the study population was diagnosed in the second half of pregnancy. As HbA1c reflects glycaemic control over the preceding 12 weeks, the booking HbA1c will typically reflect the glycaemic levels in earlier gestation when GDM may not have developed. It is therefore not surprising that HbA1c parameters such as booking HbA1c and the last HbA1c before delivery were not predictive of PNM in GDM as have been shown with pre-gestational diabetes (21,143,145). The predictive nature of 3rd trimester PPG for PNM indicates the advantage of plasma glucose profiles, which reflects short-term changes in glycaemia as a marker of glycaemic control in GDM compared with pre-gestational diabetes. It also indicates that greater efforts are needed to ensure that patients achieve target PPG levels in GDM patients.

Fetal anomalies were documented in 5 GDM pregnancies; 2 in the IGT and 3 in the DM group. Treatment modality as a possible aetiology is unlikely, as patients were only commenced therapy well after the first trimester. Indeed logistic regression analysis in the cohort of all GDM subjects did not identify the use of OGLAs as predictive of fetal anomaly.

The GDM subjects, similar to pre-gestational type 2 DM subjects, also showed similar rates of neonatal hypoglycaemia regardless of 3rd trimester treatment modality. Indeed, as with type 2 DM patients and for the same reasons, OGLAs use in the 3rd trimester was not associated with neonatal hypoglycaemia.

It is not clear why the GDM group that was converted from OGLAs to insulin (group 3) had a significantly lower rate of macrosomia compared with other treatment groups, but this is the likely explanation for the significantly lower rate of caesarean section in group 3 subjects, as large babies are an indication for caesarean section. The finding by Homko et al (36) of an association between ethnicity and macrosomia is collaborated by the 4 times higher risk of macrosomia in the cohort of black women with GDM compared with their counterparts of mixed ancestry.

The association between obesity and glucose intolerance in pregnancy is highlighted, as the mean BMI in all the GDM study groups was greater than 30

$kg/m^2$ albeit at the time of booking. The high mean BMI of our study population also provides a rational basis to initiate lifestyle measures that may limit further weight gain. This may in turn reverse glucose intolerance with health benefits beyond improved glycaemic control as maternal obesity per se is associated with adverse pregnancy outcomes such as macrosomia, congenital anomalies and hypertensive disorders (150). Indeed, the excellent PNM in patients treated with diet alone underscores the importance of diet as a treatment modality.

The reasons for the very low HbA1c levels (tables 5h and 5i) are not apparent. The main causes other than laboratory error and aggressive glycaemic control are variant haemoglobins C, D, S which interfere with the assay for HbA1c on high performance liquid chromatography (HPLC) resulting in falsely low results and conditions associated with accelerated red cell turnover such as haemolysis or haemorrhage which lead to reduced red cell life span (151). Lipaemia, malignancies, retroviral infection, anti-retroviral drugs and acetylsalicylic acid use may also interfere with the assay for HbA1c and lead to falsely low HbA1c levels (151). Data on maternal hypoglycaemic episodes during pregnancy, haemoglobin genotypye and indices of anaemia were not however captured.

This study similar to all retrospective reviews has a number of limitations:

Data on maternal complications such as frequencies of hypoglycaemia and diabetic retinopathy were not captured.

The data capture on respiratory difficulties did not allow for the identification of neonates with respiratory distress as all forms of respiratory difficulties were captured including transient treatment with facemask oxygen.

Finally, there were instances where data was missing for important variables in the untreated type 1 DM patients. Outcome data in the treated patients in contrast were well recorded.

## Chapter 6: Conclusions and Recommendations

This large retrospective study has highlighted that the pre-gestational types 1 and 2 DM subjects booked with poor glycaemic control underscoring the need for improved pre-conception care in Cape Town. This requires the implementation of specifically designed guidelines and strategies and may best be achieved using dedicated clinics run by a multidisciplinary team including endocrinologists, obstetricians, diabetic educators and dieticians. These clinics should aim to educate women with diabetes who are contemplating pregnancy and promote attitudes that will not only lead to the attainment of target glycaemic goals before conception but also to the maintenance of adequate glycaemia in pregnancy.

Guidelines should include discontinuation of potentially teratogenic agents before pregnancy. Consequently anti-hypertensives like enalapril and ramipril should be substituted with safer agents like methyldopa, nifedipine or hydralazine. Detrimental habits such as smoking and alcohol consumption in pregnancy should be discouraged. Patients require education in self-blood glucose monitoring. Pre-pregnancy contraception should be the norm in women of reproductive age and such contraception should be continued until adequate blood glucose control is achieved.

In a situation of a large diabetic population and inadequate complement of trained personnel as in Cape Town, it is strongly recommended that all women of reproductive age be on an effective contraceptive except where contra-indicated and be referred to dedicated clinics for further assessment when pregnancy is desired.

Although, retrospective in nature, this study supports the notion that metformin and probably glibenclamide are not teratogenic. Whilst the use of OGLAs in GDM was not attended with increased PNM, (indeed there was no PNM in the subgroup of GDM subjects treated with OGLAs only), it is critical to replace OGLAs in particular glibenclamide with insulin once patients with pre-gestational type 2 diabetes have booked in pregnancy. Metformin at doses not exceeding 1700 mg may be safely recommended throughout gestation for gestational and pre-gestational type 2 DM; glibenclamide at dose not exceeding 10 mg can be recommended in GDM but not pre-gestational type 2 DM pregnancies. Consequently, subjects with type 2 DM on OGLAs other than metformin at booking should be converted to insulin for the rest of gestation.

This study also highlights the importance of adequate glycaemic control in preventing adverse pregnancy outcomes. While the last HbA1c before delivery was significantly predictive of PNM in pre-gestational type 2 DM, only the 3$^{rd}$ trimester PPG level was predictive of PNM in the GDM subjects. It is thus recommended that fasting and post-prandial plasma glucose levels be used

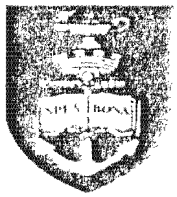
rather than HbA1c in assessing glycaemic status in patients with GDM, a condition that often truly exists only in the latter half of pregnancy.

In this cohort of patients from Cape Town, treatment of newly diagnosed diabetes in pregnancy had clear benefits with PNM rates lower than that of untreated diabetes subjects, but treated and untreated GIGT subjects had similar PNM rates. Stratification of GIGT subjects by diagnostic FPG or 2hour OGTT plasma glucose value did not identify any group at greater risk of increased PNM or morbidity. To what extent GIGT should be treated in societies where there are competing demands on very limited health budgets needs to be answered particularly where universal rather than selective screening for GDM is recommended.

Strategies to improve follow up at 6 weeks post delivery for a repeat OGTT are needed to enable the identification of those subjects with persistent glucose intolerance who require appropriate management.

## APPENDIX 1

UNIVERSITY OF CAPE TOWN



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06 October 2004

REC REF: 375/2004

Dr CO Ekpebegh
Medicine

Dear Dr Ekpebegh

AUDIT OF DIABETIC PREGNANCIES MANAGED AT GROOTE SCHUUR HOSPITAL, CAPE TOWN, SOUTH AFRICA DURING THE PAST DECADE

*Thank you for submitting your study to the Research Ethics Committee for review.*

*It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study on the 04 October 2004.*

*Please assure confidentiality is maintained of all information that may be accessed from folder.*

Please quote the REC. REF in all your correspondence

Yours sincerely

PROF. T. ZABOW
CHAIRPERSON

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