Pregnancy outcome in patients with pregestational and gestational diabetes attending Groote Schuur Hospital, Cape Town, South Africa

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Background. The burden of diabetes mellitus (DM) has increased dramatically worldwide. The association between poorly controlled DM and poor pregnancy outcomes has been well described.

Objectives. To describe the pregnancy outcomes of patients with pregestational and gestational DM attending Groote Schuur Hospital, Cape Town, South Africa.

Methods. A retrospective audit was undertaken of all women with pregestational and gestational DM (GDM) who attended Groote Schuur Hospital obstetric care from 1 September 2010 to 31 August 2011. Information routinely collected at booking and during the rest of pregnancy was entered onto a data abstraction form. Patients diagnosed with GDM were further subdivided into two groups, GDM and impaired glucose tolerance (IGT), depending on the oral glucose tolerance test results.

Results. A total of 725 diabetic pregnancies were managed: 35 women had type 1 DM (T1DM), 194 had type 2 DM (T2DM), 192 had GDM and 304 had IGT. The median glycated haemoglobin (HbA1c) value at booking was highest for T1DM, followed by T2DM and lastly GDM. Overall, 10.7% of women had pre-existing hypertension and 9.8% developed pre-eclampsia (PET). The preterm delivery rate (before 38 weeks) was 68.8% for women with T1DM, 38.7% for those with T2DM, 34.9% for those with GDM and 22.4% for those with IGT. The caesarean section rate exceeded 50% in all groups. The overall perinatal mortality rate was 2.5% (25/1,000 births) for the study population, with T1DM and T2DM contributing most deaths (6.4% and 4.2%). The overall rate of congenital malformations was 2.4% (n=18 cases), but the rate was 5.7% for patients with T1DM and 4.6% for those with T2DM.

Conclusion. The audit demonstrated outcomes similar to those in the developed world, with major congenital malformations, unexplained stillbirths and PET accounting for the majority of perinatal deaths. Stricter control with the aim of achieving lower or normal HbA1c levels before conception may be the only intervention that could bring about change.


The number of people with diabetes mellitus (DM) continues to increase, with projections suggesting a rise from 429 million in 2017 to 629 million in 2045.[1] It is notable that the greatest increase is being seen in low- and middle-income countries, where the peak prevalence occurs at a younger age.[2] By implication, an increasing number of pregnancies will be affected by DM.

In South Africa (SA), it is estimated that 3.5 million people have DM, with many more undiagnosed.[3] Global estimates are that type 1 DM (T1DM) accounts for ~5 - 10% of people with DM and type 2 DM (T2DM) for ~90 - 95%.[4] DM2 is frequently undiagnosed until pregnancy, and incorrectly labelled as gestational DM (GDM). It is believed that women with undiagnosed T2DM carry a much higher maternal and fetal risk than those with GDM. In 2008 - 2009, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) and the American Diabetes Association suggested that similar criteria can be used to diagnose T2DM in pregnancy and outside of pregnancy.[4]

GDM is defined as ‘glucose intolerance with onset or first recognition during pregnancy’. [3] Currently 1 in 7 births are affected by GDM globally.[5] Although these pregnancies do not carry the same risks as pregestational DM, recent literature has shown that babies born to mothers with GDM are hyperinsulinaemic, often macrosomic, and at increased risk of shoulder dystocia, birth trauma, caesarean delivery and neonatal hypoglycaemia.[6]

GDM furthermore becomes a general public health issue, since women with GDM have a 60% probability of developing T2DM later in life, with an annual conversion rate of ~10% per year.[7] Huddle,[8] in his study on the management and outcome of DM in pregnancy at Chris Hani Baragwanath Hospital in Johannesburg, SA, during 1992 - 2002, reported that patients who booked early and were exposed to treatment for the duration of their pregnancies had a good pregnancy outcome, similar to those in high-income countries. However, late presentation was associated with a very high overall perinatal mortality rate (PNMR) of 15.6%, compared with 3.7% for the treated group. There were no significant differences between the PNMR for T1DM, T2DM and GDM in the treated groups (4.2%, 3.9% and 2.8%, respectively). The combined PNMR for the treated and control groups was 6.3%.

Ekpebgh et al.[9] found a PNMR of 5% in patients with T2DM at Groote Schuur Hospital (GSH) in Cape Town, SA. Increased rates were directly associated with high booking glycaated haemoglobin (HbA1c) levels. Interestingly, treatment throughout pregnancy with glibenclamide was also associated with increased perinatal mortality, although no clear explanation for this could be found. Perinatal mortality was not increased in patients treated with metformin.

Objectives
To assess fetal and maternal outcome for patients at GSH with GDM
and pregestational DM, and specifically mild GDM, also referred to as impaired glucose tolerance (IGT), to assess whether care for this group of patients could be downgraded to secondary level. The primary outcomes looked at were miscarriages, congenital abnormalities, shoulder dystocia, macrosomia and perinatal mortality. Maternal outcomes included need for induction of labour, incidence of pre-eclampsia (PET), preterm delivery and caesarean section.

Methods
Study design and population
This was a retrospective descriptive study of all patients who attended GSH with either pre-existing or newly diagnosed GDM over a period of 1 year (1 September 2010 - 31 August 2011). Diabetes was considered pregestational if it existed before conception and gestational if it was first diagnosed during pregnancy.

At GSH and within its drainage area, the antenatal diabetes screening programme calls for screening at 16 weeks’ gestation, and again at 24-28 weeks if the first test was normal. GDM was diagnosed if the patient had a fasting blood glucose level >5.5 mmol/L or a 2-hour level of >7.8 mmol/L using a 75 g oral glucose tolerance test (OGTT). Patients were further divided into two groups based on the OGTT results: IGT if the fasting blood glucose level was 5.5-7 mmol/L and the 2-hour value 7.8 - 11 mmol/L, and GDM if the fasting level was >7 mmol/L and the 2-hour level >11 mmol/L. For the purpose of this article, all patients diagnosed for the first time in pregnancy were regarded as having GDM, but data were analysed separately for IGT and GDM.

Data collection
Data were entered into a database using Microsoft Office Excel 2007 (Microsoft, USA). Data captured included past obstetric history, type of diabetes, initial HbA1c level, gestational age at booking, type of treatment, maternal complications, presence or absence of fetal abnormalities, birth weight, level of glucose control, incidence of PET, mode of delivery and pregnancy outcome. Data were anonymised upon entry into the database.

Statistical analysis
Maternal characteristics, clinical measures and outcomes were summarised using descriptive statistics. Continuous variables were expressed as medians with interquartile ranges, and categorical variables were presented as frequencies and percentages. The Kruskal-Wallis test was used to compare differences in non-normally distributed continuous variables between DM classification groups. The Wilcoxon rank-sum test was used for comparisons of two groups where applicable. For associations between categorical variables, either Pearson’s χ² test or Fisher’s exact test was applied depending on the distribution of frequencies. A p-value of <0.05 was considered statistically significant. Analysis was performed in Stata 13 (StataCorp, USA).

Ethical considerations
The study protocol was submitted for ethical approval to the Human Research Ethics Committee (HREC) of the University of Cape Town (ref. no. 377/2012). Consent and institutional approval were obtained from GSH as the site of the study, and the database was subsequently registered with the HREC (ref. no. R010/2016).

Protocol for clinical management
Pregestational DM
Women with pregestational DM were admitted to a single antenatal ward for review and optimisation of treatment. The baseline work-up included HbA1c levels at booking, serum creatinine, urea and electrolytes, and a 24-hour urinary protein test. A fetal ultrasound scan to confirm viability and to assess for fetal anomalies was performed in patients assessed before 22 - 24 weeks’ gestation. Dietary counselling and education on diabetes was provided by a trained dietician, as well as nursing and medical staff.

In patients with T2DM all oral therapy other than metformin was discontinued, and if target blood glucose levels were not met after 1 day in hospital (fasting levels <5.5 mmol/L and 2-hour postprandial levels <6.7 mmol/L), either insulin was added to the metformin or metformin was replaced by insulin, similar to the protocol used by Ekpbegh et al.[9]

Patients with T1DM were converted to a multiple daily insulin regimen of regular and intermediate-acting insulin. Subsequent adjustment of the doses was based on fasting and postprandial values.

GDM (GDM and IGT)
All patients diagnosed with GDM and IGT received dietary counselling from a trained dietician, and fasting and postprandial glucose levels were assessed. HbA1c was measured if either of the two OGTT values fell in the overt diabetic range. If the glycaemic targets (fasting glucose <5.5 mmol/L or 2-hour postprandial value <6.7 mmol/L) were not achieved, treatment was commenced: first metformin, and then insulin if indicated.

All patients on treatment were asked to return 1 week later to assess response and compliance. Thereafter, patients were seen at a dedicated diabetes clinic fortnightly until 32 weeks, and then weekly until delivery at 38 weeks. Ultrasound scans were done at 22 weeks to screen for fetal anomalies and at 32 and 36 - 37 weeks for growth checks. HbA1c levels were repeated at 6 - 8-week intervals and delivery was timed for 38 weeks’ gestation. Women were offered induction of labour in the absence of an indication for caesarean section (CS) and evidence of macrosomia on the ultrasound scan. CS was offered if the estimated fetal weight exceeded 4 000 g and the abdominal circumference exceeded the 97th centile.

Results
During the study period there were 5 551 deliveries at GSH, which provides care for all high-risk pregnancies and 39 203 deliveries in the Metro West, the health district that GSH serves as the tertiary level hospital. There were 725 DM patients with 740 births at GSH; the majority had GDM and IGT (68.6%).

Maternal profiles (Table 1)
The median gestational age at booking was <20 weeks for all the groups. Compared with the other three groups, women in the T1DM group were younger and had a lower BMI but a higher median HbA1c level at booking. More than a third of T1DM patients had an initial HbA1c >10% at booking.

A substantial proportion of patients with T1DM (50%) and 41.7% of patients with T2DM had a daily urinary protein value >300 mg/d. However, no investigations other than routine urinary dipstick testing were done to rule out other causes for proteinuria.

Chronic hypertension was found to be most prevalent in the T2DM group. The incidence of PET, although not significant, was highest in T1DM.

Treatment
As expected, all patients with T1DM received insulin, while 99% of the T2DM group and 96% of patients with GDM received either metformin...
or insulin. A third of patients with IGT received some form of treatment: metformin alone, metformin and glibenclamide, or insulin.

There was one maternal death at 25 weeks’ gestational age from respiratory failure due to the respiratory virus (H1N1).

The T1DM group had the highest preterm delivery rate, but the lowest rate of successful induction of labour. Although the caesarean section rate exceeded 50% in all groups, the T1DM group had the highest rate.

### Fetal and perinatal outcome (Tables 2 and 3)

Of the pregnancies in the T1DM group 5.7% (n=2) ended in miscarriage, which was a higher rate than in the other groups. The IGT group suffered very few miscarriages (0.3%, n=1).

Fetal anomalies were more common in the T1DM (5.7%, n=2) and T2DM (4.6%, n=9) groups than in the GDM and IGT groups, which had rates comparable to the general population (1.5%, n=3 and 1.3%, n=4, respectively). Similarly, the PNMR was higher in the T1DM and T2DM groups (6.4% (n=2) and 4.1% (n=8), respectively) and lower in the GDM and IGT groups (both 1.6% (n=3 and n=5)).

The overall PNMR for the study population was 2.5% (25/1000 births). The rates for both GDM and IGT were much lower than for the pregestational groups, and in fact lower than the background PNMR for SA (3.1%) and the Metro West (2.6%).[10]

The macrosomia rate was similar across all the groups. Of the 5 deliveries that were complicated by shoulder dystocia, 3 had a good outcome for the baby. In the remaining 2 cases, one baby born to a mother with T1DM had hypoxic ischaemic encephalopathy (birth weight 3675 g). The other baby, born to a mother with GDM, sustained a fractured humerus but also had dysmorphic features, microcephaly and an absent corpus callosum. This baby weighed 3485 g.

Table 3 shows the correlating HbA1c values at booking for the different anomalies.

### Discussion

The PNMR in the pregestational DM group was higher than that for the background population, in contrast to the GDM and IGT groups, in which a lower PNMR was observed. The booking HbA1c level for the T1DM patients was unacceptably high and almost 6% of these patients had miscarriages. The fetal anomaly rate was higher in both the T1DM and T2DM groups than in the GDM and IGT groups, where the fetal anomaly rate was lower than the background rate.

Although the PNMR differs between countries, it remains significantly higher in pregestational diabetes than in non-diabetic and gestational diabetes groups, which is in keeping with our findings. Our PNMR for the pregestational DM group was similar to

### Table 1. Summary of maternal characteristics

<table>
<thead>
<tr>
<th></th>
<th>T1DM (N=35)</th>
<th>T2DM (N=194)</th>
<th>GDM (N=192)</th>
<th>IGT (N=304)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at booking</td>
<td>25 (22 - 30)</td>
<td>33 (29 - 36)</td>
<td>32 (28 - 36)</td>
<td>30 (26 - 35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GA at booking</td>
<td>20 (37.1)</td>
<td>84 (43.3)</td>
<td>58 (30.9)</td>
<td>78 (25.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI at booking</td>
<td>10 (62.5)</td>
<td>18 (17)</td>
<td>38 (27)</td>
<td>88 (34.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>7 (2.9)</td>
<td>39 (20.1)</td>
<td>20 (10.4)</td>
<td>18 (5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>17 (35.4)</td>
<td>79 (18.3)</td>
<td>38 (36 - 38)</td>
<td>38 (36 - 38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Successful IOL</td>
<td>4 (11.8)</td>
<td>36 (18.6)</td>
<td>52 (27.1)</td>
<td>88 (30.0)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; GDM = gestational diabetes mellitus; IGT = impaired glucose tolerance; IQR = interquartile range; GA = gestational age; BMI = body mass index; HbA1c = glycated haemoglobin; PET = pre-eclampsia; DUP = daily urinary protein; CS = caesarean section; IOL = induction of labour.

*Overall PNMR for the four groups = 2.5%.

### Table 2. Fetal and perinatal outcomes for different types of diabetes in pregnancy

<table>
<thead>
<tr>
<th></th>
<th>T1DM (N=35)</th>
<th>T2DM (N=194)</th>
<th>GDM (N=192)</th>
<th>IGT (N=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriages, n (%)</td>
<td>2 (5.7)</td>
<td>5 (2.5)</td>
<td>7 (3.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Fetal anomalies, n (%)</td>
<td>2 (5.7)</td>
<td>9 (4.6)</td>
<td>3 (1.5)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Stillbirths, n (%)</td>
<td>2 (6.4)</td>
<td>6 (3.1)</td>
<td>1 (0.5)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Early neonatal deaths, n (%)</td>
<td>0</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>PNMR*</td>
<td>6.4</td>
<td>4.1</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Macrosomia (birth weight &gt;4000 g), n (%)</td>
<td>3 (8.5)</td>
<td>16 (8.2)</td>
<td>27 (14.1)</td>
<td>28 (9.2)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>1 (3.2)</td>
<td>0</td>
<td>3 (1.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; GDM = gestational diabetes mellitus; IGT = impaired glucose tolerance; PNMR = perinatal mortality rate.

*Overall PNMR for the four groups = 2.5%.
Table 3. Spectrum of fetal anomalies and HbA1c values at booking (where available)

<table>
<thead>
<tr>
<th>Fetal anomaly</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1DM</td>
<td></td>
</tr>
<tr>
<td>Univentricular heart</td>
<td>11.7</td>
</tr>
<tr>
<td>Multicystic dysplastic kidney</td>
<td>6.7</td>
</tr>
<tr>
<td>T2DM</td>
<td></td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>9.4</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>10.3</td>
</tr>
<tr>
<td>Cleft palate, skeletal abnormality</td>
<td>11.9</td>
</tr>
<tr>
<td>Encephalocoele</td>
<td>11.7</td>
</tr>
<tr>
<td>Hypoplastic left heart</td>
<td>10.5</td>
</tr>
<tr>
<td>Ventricular septal defect, normal karyotype</td>
<td>8.1</td>
</tr>
<tr>
<td>Multicystic dysplastic kidney</td>
<td>12</td>
</tr>
<tr>
<td>Ventriculomegaly</td>
<td>12.4</td>
</tr>
<tr>
<td>Congenital cystic adenoid malformation</td>
<td>8.2</td>
</tr>
<tr>
<td>GDM</td>
<td></td>
</tr>
<tr>
<td>Multiple abnormalities</td>
<td>6.4</td>
</tr>
<tr>
<td>Pelvic cyst</td>
<td></td>
</tr>
<tr>
<td>Semilobar holoprosencephaly</td>
<td>8.5</td>
</tr>
<tr>
<td>IGT</td>
<td></td>
</tr>
<tr>
<td>Ventriculomegaly</td>
<td></td>
</tr>
<tr>
<td>Cardiac abnormality</td>
<td></td>
</tr>
<tr>
<td>Congenital cystic adenoid malformation</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect, truncus arteriosus</td>
<td></td>
</tr>
<tr>
<td>45,XX Robertsonian translocation</td>
<td></td>
</tr>
</tbody>
</table>

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; GDM = gestational diabetes mellitus; IGT = impaired glucose tolerance

that reported for France in 2001 (4.5%) and higher than reported in the UK in 2004 (2.3%). These figures are still much higher than the background PNMRs for these countries.[11,12]

Data on the outcome of IGT, GDM and pregestational DM in SA include the studies by Huddle, reporting an overall PNMR of 6.3% for pregestational DM,46 and Ekpebegh et al.,47 which did not include patients with T1DM but reported a PNMR of 5% for T2DM.

Our finding of a higher miscarriage rate in T1DM and higher fetal anomaly rates in both T1DM and T2DM is consistent with the international literature and probably related to poor glycaemic control, as reflected by the high HbA1c values at booking. In our study, the HbA1c level in all the T2DM cases with fetal anomalies was >8%, which is in keeping with a French survey48 which found significantly higher preterm delivery and congenital anomaly rates if the initial HbA1c value was >8%.

These data emphasise the fact that although DM does not feature among the top 10 causes of stillbirths in SA, strategies need to be employed to decrease the high risk that remains in pregestational DM. This is particularly important in view of the fact that DM is becoming increasingly common in women of childbearing age in SA. In agreement with the conclusion reached in the report of the 2015 National Pregnancy in Diabetes Audit in England, Wales and the Isle of Man,49 it is essential that attention be given to pre-pregnancy counselling in this group. This may prove difficult, because most pregnancies in SA are unplanned. Potential solutions include a general approach to stricter glycaemic control outside of pregnancy, greater attention to addressing family planning in women with DM, who generally attend primary care clinics, and finally setting up a referral pathway at multidisciplinary clinics in all our major centres for women with DM who are planning a pregnancy. These clinics would focus on education and optimisation of care, including assessment of renal function and degree of retinopathy, ensuring the introduction of folate and iron supplementation, a comprehensive review of medication that may be teratogenic, and achievement of optimal glycaemic control before conception.

One of the main objectives of this study was to determine the outcome for IGT and establish whether care for this group of patients could safely be downgraded to secondary level. Following the initial results, which confirmed excellent outcomes in this group of patients, care was indeed downgraded to secondary level. A random blood glucose (RBG) measurement is done at every visit, and patients are only referred to tertiary care for formal fasting and postprandial readings if the RBG is >6.7 mmol/L. This strategy is also employed in other countries, where care is downgraded even further to midwife or general practitioner level, and is deemed to be safe.[10]

It is likely that at least 40% of our patients diagnosed with GDM actually had undiagnosed T2DM, as reflected by the booking HbA1c.

It is notable that almost without exception patients with poor outcomes had an HbA1c of >6.5% at booking.

HbA1c is known to be much lower in early and late pregnancy than in non-pregnant women. What appears to be a ‘normal’ HbA1c value is therefore in fact a high value for pregnancy.[13]

Although compared with the IGT group more patients with GDM required treatment, the number of fetal abnormalities, the rate of PET and the PNMR were similar between the two groups and better than the rates for T1DM and T2DM. The finding of similar outcomes for the GDM and IGT groups was surprising. One reason for this could be that the OGTT was done earlier at 16 weeks in all patients who qualified for screening, which led to earlier diagnosis and therefore earlier initiation of treatment. Treatment was also stepped up aggressively if target glucose levels were not maintained. More than 90% of patients with GDM were treated either with metformin (and additional glibenclamide in a few cases) or with insulin.

The rate of PET is reported to be increased in pregestational diabetes in the literature, but we found this to be true only for the T1DM group in our population (20.0%). Both GDM and T2DM showed no increase above the background incidence of PET in our setting. It is widely reported that the background incidence of PET is much higher in sub-Saharan Africa than in developed countries,[14] but this does not explain why T2DM patients in our population do not also have an increased rate.

Another change since 2011 is follow-up of patients with GDM. Although patients are still followed up at tertiary level, admission has become impossible owing to bed constraints, and dietary counselling by the attending doctor, followed a week later with fasting and post-breakfast finger-prick blood glucose levels, is done on an outpatient basis. If these are high, oral treatment is commenced and admission arranged to establish whether insulin is required. This new regimen could potentially lead to significant delay in treatment compared with the previous situation.

The IADPSG has in the meantime published new criteria for the diagnosis of GDM.[15] It should be noted that neither GSH nor the Western Cape Province nor the SA national guidelines have adopted these new guidelines as yet.

Study limitations

Our study had several limitations. This was a retrospective review and the number of patients with T1DM included was small. In addition, knowing the gestational age at which the OGTT was done would have added valuable information in terms of classification of type of DM and determining reasons for poor outcome.
Conclusions
These results indicate the need for active family planning and optimisation of glycaemic control in women with DM of childbearing age. Furthermore, we suggest that women diagnosed with IGT in pregnancy, can be managed safely at secondary-level care. Further audits on outcome, especially in the GDM and IGT groups, are therefore extremely important to ensure that the changes brought about have not compromised care.

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Author contributions. HVZ and NSL conceptualised and designed the study and drafted the manuscript. HVZ collected the data with help from the registrars in the unit at the time.

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