

# An audit of stillborn babies in mothers with diabetes mellitus at a tertiary South African Hospital

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**Objectives and design:** This study is a retrospective audit spanning six years following the implementation of a new guideline on the management of diabetes in pregnancy. It aims to describe the patient profile of pregnancies complicated by diabetes and stillbirth.

**Setting:** The study was performed in Tygerberg Hospital, Cape Town, a secondary and tertiary referral centre.

**Subjects:** Fifty-eight pregnancies were complicated by stillbirth (> 500 g). Outcome measures: the patient profile, gestational age, co-morbidities, foetal/placental monitoring and avoidable factors were described.

**Results:** Many patients (32%) booked after 24 weeks' gestation and missed appointments were common (26.2%). Stillbirths ascribed to diabetes constituted 2.3% of all stillbirths at the hospital during the study period. Of the stillbirths 28.1% had Type I diabetes mellitus (DM), 64.9% had Type II and 7.0% were in patients with gestational diabetes. The median HbA1c at delivery was 8.4% (range 6.0–14.1%). In the Type II group, 31 (77.5%) of the stillbirths occurred after 36 weeks, while those among the Type I cases ranged from 26 to 38 weeks.

**Conclusion:** Stillbirths amongst pregnant women with diabetes constituted a small percentage of the total stillbirth burden. Emphasising the importance of appropriate antenatal care to women with diabetes and increased surveillance from 36 weeks' gestation may lower the number of stillbirths.

**Keywords:** diabetes mellitus, gestational diabetes, pregnancy, stillbirth

## Introduction

Glucose metabolism changes in pregnancy. Fasting levels of serum glucose are decreased while post-prandial levels are increased compared with non-pregnant women. Glucose tolerance decreases progressively after the first trimester. Physiological insulin resistance is brought about by placental hormones such as human placental lactogen, glucagon and cortisol. Ultimately insulin production is almost doubled to maintain euglycaemia. Gestational diabetes mellitus (GDM) develops when there is a mismatch between this increased insulin demand and the ability of the maternal pancreas to appropriately increase its production of insulin, due to a reduced beta-cell reserve. This also explains the increased therapy requirements of established (pre-gestational) diabetes.

The incidences of both Type II diabetes mellitus (DM) and GDM are rising. This can be attributed first to the pregnant population becoming older and more obese. Rising levels of obesity that correspond with high-calorie diets and decreased levels of physical activity affect many countries, including South Africa.<sup>1,2</sup> Furthermore, the diagnostic thresholds for the diagnosis of GDM have been lowered following the sentinel ACHOIS and HAPO studies, which showed composite benefit by initiating intervention at lower glucose levels.<sup>3–5</sup>

The management of patients with diabetes in pregnancy at Tygerberg Hospital has previously been carefully described and the guidelines are on a par with international recommendations.<sup>6–8</sup>

All inborn perinatal deaths at Tygerberg Hospital are discussed at a weekly, multidisciplinary meeting. Apart from a primary cause of death, associated patient-related, medical and administrative

avoidable factors are identified. Unlike true GDM, pre-gestational diabetes is associated with the complication of sudden unexplained intra-uterine death (IUD). This audit was performed to re-examine the stillbirths related to maternal diabetes and determine the timing and factors associated with this outcome.

## Materials and methods

This study was a retrospective audit spanning a six-year period that followed implementation of a new Tygerberg Hospital guideline on the management of diabetes.<sup>7</sup> Patients included were managed at Tygerberg Hospital, a combined secondary/tertiary referral unit in Cape Town, South Africa, where all perinatal deaths are discussed and entered into the national Perinatal Problem Identification Program (PPIP) database.

The diagnosis of pre-gestational diabetes (Type I or II) was made when the history was known. Gestational diabetes was regarded as any new onset hyperglycaemia in pregnancy. The precise diagnostic criteria (based on the NICE guidelines) are contained in the provincial guideline on diabetes mellitus in pregnancy (Western Cape), which has been fully described in a recent publication.<sup>7</sup> Care was taken to differentiate this from undiagnosed pre-gestational diabetes (i.e. when any one of the WHO Criteria for overt DM were met), although this differentiation was not always possible. A stillbirth was defined as asystole in a newborn of > 500 g birth weight. Viability was set at 27 weeks' gestation. The gestational age at diagnosis of the intra-uterine death was used for each pregnancy. Delivery was offered as standard practice at 38 weeks' gestation.<sup>7</sup> The principal investigator retrieved the records and re-linked the file numbers to all diabetes-associated stillbirths over six years. File records were then scrutinised using a data sheet with study numbers only.

**Table 1:** Maternal characteristics at study entry (data as median/range or n/%)

Age (years) (n = 57)*	31 (17–44)
Gravidity (n = 57)*	3 (1–11)
Parity (n = 57)*	3 (0–11)
Body mass index kg/m <sup>2</sup> (n = 48)*	
< 20	0 (0.0)
20.1–25.0	7 (14.5)
25.1–30.0	9 (18.8)
30.1–40.0	25 (52.1)
40.1–50.0	2 (4.2)
> 50.1	5 (10.4)
Chronic hypertension (n = 56)*	15 (26.7)
Any previous pregnancy loss ≥ 24 weeks (n = 56)*	8 (14.3)
Previous pregnancy loss ≥ 24 weeks due to diabetes (n = 56)*	3 (5.4)
Previous baby ≥ 4 kg (n = 50)*	4 (8.0)
Gestation at booking (weeks) (n = 50)*	17 (5–38)
Booked < 24w0d (n = 50)*	34 (68.0)
Gestation at entry to appropriate level of care (n = 53)*	26 (6w0d–40w0d)

\*Information was not available for all 59 patients.

Data were analysed using standard IBM SPSS® version 24 (IBM Corp, Armonk, NY, USA). Descriptive statistics were used to describe the data. For continuous variables, the results are expressed in terms of means, standard deviations, medians and ranges. Frequency tables (n, %) were used to describe some categorical variables.

The study was approved and registered by the Human Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University (S15/08/185). A waiver of consent was granted for this retrospective audit.

## Results

This study was conducted from January 1, 2010 to December 31, 2015 during which time a total of 59 stillbirths (including one set of twins) were attributed to DM. These 59 stillbirths constituted 2.3% of all stillbirths and 0.14% of the 43 095 births (> 500 g) during the study period.<sup>9</sup> The maternal characteristics at study entry are shown in Table 1.

After re-examination of factors known to be associated with stillbirth, patients were sub-divided into the following groups according to the gestational age at diagnosis of the stillbirth (58 patients had available information). Selected pertinent facts are reported in Table 2.

Four patients (6.9%) were known to have human immunodeficiency virus. Three of these patients were using anti-retroviral therapy and one used peri-partum prophylaxis prior to long-term anti-retroviral therapy becoming the standard management in pregnancy. The classification of deaths in the different categories of DM is depicted in Table 3.

Thirty-one (77.5%) of the deaths amongst the Type II group occurred after 36w0d, while those among the Type I cases ranged from 26 weeks to 38 weeks' gestation. Treatment regimens are categorised in Table 4.

Long-term glucose control was monitored using glycosylated haemoglobin (HbA1c). A pre-gestational HbA1c was available in nine patients (median 9.2%, range 7.5–11.6). The median booking HbA1c value (n = 45) was 8.3% (range 5.9–12.0%) and the median pre-delivery value (n = 45) was 8.4% (range 6.0–14.1%).

A foetal abnormality (including growth aberrations) was noted in 20 (40%) babies on either antenatal ultrasound or post-natal examination. These are depicted in Table 5. Birth weights for five babies met the criteria for small-for-gestational-age. The birth weights for four (7.1%) babies plotted below the 10th centile and one baby had a weight below the 3rd centile. The gestational ages of these 5 babies ranged from 28w1d to 40w5d. Macerated babies were noted in 48 cases (85.7%). In 21 (65.6%) of the 31 patients with available placental histology, diabetic changes were detected.

## Discussion

Stillbirths ascribed to diabetes mellitus are a matter of concern to obstetricians worldwide. International data from an audit on pregnancy outcomes in diabetic patients in the United Kingdom estimated the stillbirth rate to be 12.8 per 1 000 births to all women with diabetes.<sup>10</sup> Stillbirths are generally associated with pre-gestational diabetes and not with true GDM, but precise classification may be challenging due to several confounding factors. However, it is particularly important to detect undiagnosed pre-gestational diabetes in pregnancy as the risk profile differs for the mother and the foetus.

Available data for South Africa come from two publications. In 2005 Huddle published an 11-year audit of the outcomes of pregnancy in diabetic women in Soweto.<sup>11</sup> He noted 2.8% stillbirths amongst women with GDM as well as 3.9% and 1.8% stillbirths in women with Types I and II diabetes respectively. A more recent publication by Hall et al. from Tygerberg Hospital, Cape Town found no stillbirths amongst women with Type I diabetes, as well as 6.5% and 12% stillbirths amongst women with Types II and gestational diabetes respectively.<sup>6</sup> The latter study covered only 12 months and less attention was given to differentiating undiagnosed pre-gestational diabetes from true GDM.

In the index study an accurate number of all pregnancies managed with diabetes could not be obtained from the various clinics where the audit was performed. When expressed as a stillbirth rate for all births > 500 g from 2010 to 2015 the figure was 1.39/1 000. Once broken down into annual rates over the six-year period, the figure varied from 0.89/1 000 to 2.12/1 000.<sup>9</sup> The stillbirth rate may be overrepresented in these figures due to the fact that the study hospital serves as a secondary and tertiary referral centre.

A pregnant patient with diabetes carries an increased risk of stillbirth due to multiple factors. For this reason, women with diabetes who are contemplating pregnancy should be well educated concerning pre-conception glycaemic control and folate supplementation, early booking for antenatal care and meticulous compliance with the care-plan. In this study 11% of patients had experienced a previous pregnancy loss (from any cause), 32% booked late (≥ 24 weeks' gestation) for care and > 50% denied clinicians an adequate opportunity to intervene meaningfully. The gestation-dependant relative risk increases as follows: RR 4.95 (95% CI 2.61–2.84) at 32–34 weeks, 3.77 (95% CI 3.42–4.16) at 35–36 weeks, 5.75 (95% CI 5.43–6.09)

**Table 2:** Gestation-specific analysis\*

Factor	< 27w0d n = 3 5.2%	27w0d-31w6d n = 10 17.2%	32w0d-33w6d n = 2 3.4%	34w0d-35w6d n = 4 6.9%	36w0d-37w6d n = 16 27.6%	38w0d-38w6d n = 16 27.6%	39w0d onwards n = 7 12.1%
<i>Diabetes mellitus (DM):</i>							
Type I	1 <sup>1</sup>	5	1	3	3	3	
Type II	2	5 <sup>2</sup>	1	1	13	13	4
GDM							3 <sup>5</sup>
<i>DM complications:</i>							
Retinopathy					1		
Nephropathy	1 <sup>1</sup>				1	1	
Peripheral neuropathy	1 <sup>1</sup>						
Cardiomyopathy	1 <sup>1</sup>						
Diabetic ketoacidosis	1	3	1		3	1	
<i>Hypertension:</i>							
Chronic	1	2	2			7	1
Gestational		1			1		
Pre-eclampsia				1			
<i>Umbilical artery Doppler:</i>							
Not performed <sup>3</sup>		5			8	4	4
Abnormal		1 <sup>4</sup>					
<i>Patient-avoidable factors:</i>							
Unbooked	1	2				1	2
Booked > 24 weeks		3	1		4	3	3
Missed appointments		3	1		4	3	2
Declined admission		1 <sup>4</sup>				1	
Declined induction of labour <sup>3</sup>							1
Poor treatment compliance					2		
No reaction to decreased foetal movement						2	3
<i>Medically avoidable factors:</i>							
Delayed diagnosis					1	2	2
Delayed referral <sup>6</sup>			1	1	1	2	4

\*Patients may have more than one complication.

<sup>1</sup>This patient suffered from severe target-organ involvement that included peripheral neuropathy, a forefoot amputation, nephropathy and cardiomyopathy with a left ventricular ejection fraction < 20%. This patient consented to a medical termination of pregnancy at 23 weeks' gestation.

<sup>2</sup>This includes one twin pregnancy.

<sup>3</sup>This practice is in accordance with the Provincial Guideline of the Western Cape (refer to reference<sup>7</sup>).

<sup>4</sup>This foetus developed absent end-diastolic flow in the umbilical artery at 31 weeks' gestation and declined in-patient management. Upon her return two days later, foetal distress was diagnosed and despite an emergency Caesarean section the baby was stillborn.

<sup>5</sup>No HbA1C was available to discern between GDM and Type II DM.

<sup>6</sup>This group includes three patients with absent notes referred from the private sector.

**Table 3:** Classification of deaths according to type of diabetes in pregnancy

Factor	n (%)
Type I	16 (28.1)
Type II	37 (64.9)
Gestational diabetes	4 (7.0)

Note: Patients with available information: n = 57.

at 37–38 weeks to 7.34 (95% CI 6.52–8.25) at 39 weeks and more.<sup>12</sup> In the index study half of the stillbirths were diagnosed after 37 weeks. Surveillance should therefore be increased around this time and in accordance with the NICE guidelines delivery planned at 38 weeks' gestation or earlier if indicated.<sup>13</sup> Correct patient selection for earlier delivery remains a clinical challenge, especially in the context of a resource-constrained neonatal service and known respiratory morbidity.

**Table 4:** Treatment regimens (n, %)<sup>1</sup>

None	9 (15.8%) <sup>2</sup>
Lifestyle modification (LM) only	9 (15.8)
LM and metformin	13 (22.8)
LM, metformin and glibenclamide	2 (3.5)
LM and insulin (all insulin regimens)	24 (42.1)
Any form of home monitoring	21 (36.8)

<sup>1</sup>Patients with available information: n = 57.<sup>2</sup>No opportunity to intervene (including unbooked cases).**Table 5:** Abnormalities detected on examination of the stillborn babies

Macrosomia	13
Bilateral cleft lip and palate	1
Hepatosplenomegaly	1
Hypertrophied intra-ventricular septum (post-mortem)	1
Non-immune hydrops fetalis	2
Sacral dysgenesis	1
Rocker-bottom feet and short nasal bone	1

Note: Patients with available information: n = 45.

The increased risk of a foetal loss may be due to miscarriage, congenital abnormalities, macrosomia or intra-uterine growth restriction (especially in the pre-gestational diabetic with target organ damage) or maternal complications such as DKA, preterm labour and pre-eclampsia.<sup>13</sup> A meta-analysis reported that Type I and II diabetic patients carry a similar risk for major congenital anomalies and stillbirth.<sup>14</sup> In the index study none of the six babies with anomalies diagnosed by the geneticist/pathologist postnatally had nuchal translucency or foetal anomaly scans and only two had growth scans.

In total, 29% of stillbirths in the index study were classified as macrosomic. Macrosomia results from maternal hyperglycaemia, consequent foetal hyperglycaemia and foetal hyperinsulinemia.<sup>15</sup> These foetuses are at higher risk of acidosis that may lead to myocardial dysfunction and even death. In animal studies it was found that the cardiac changes are ascribed to cardiomyocyte hypertrophy and the suppression of cardiac transcription factors in both ventricular walls, as well as the ventricular septum, and are not driven by cell proliferation or apoptosis.<sup>16</sup> Patients with known pre-gestational target-organ damage, especially nephropathy, are at particular risk of intra-uterine growth restriction;<sup>17</sup> however, none of the five mothers with small-for-gestational-age babies had nephropathy.

Regarding avoidable factors, patient compliance with antenatal care in low- to middle-income countries (LMICs) is challenging due to social demands and responsibilities. Unplanned pregnancies, not booking, late booking and irregular attendance for antenatal care deprived pregnant women of certain gestation-specific investigations and opportunities for clinicians to intervene meaningfully. In LMICs options for lifestyle modification are limited and associated economic hardship often prevents full compliance with a diabetic diet and exercise. Administrative avoidable factors centre chiefly on the capacity to screen, diagnose and manage ever-increasing numbers of pregnant women with diabetes in an obesogenic society. In this system, women diagnosed with diabetes are expected to fund

glucometers for home monitoring themselves, while the government funds the test strips.

The authors believe that, ideally, multidisciplinary centres of excellence should be established for the treatment of pregnant women with diabetes. These centres should be accessible and would include a maternal-foetal subspecialist, endocrinologist, dietician, diabetic educator and nurse practitioners, all with specific interests and experience in managing diabetes in pregnancy. Offering a single point of care will help address many of the administrative, medical and certain patient-avoidable factors highlighted in this study. This would facilitate streamlining of referrals to appropriate levels of care, aid with standardisation of assessment and monitoring of mother and foetus and ease ongoing education, tailored medical nutrition therapy and support of the patients. Where this is not available, medical staff at all levels should be familiar with and apply local protocols drafted by experts.

Although the numbers of pregnant women with diabetes are rising, stillbirths in this group constituted only a small percentage of the total stillbirth burden. In most of these cases clinicians were denied an adequate opportunity to intervene meaningfully. Better education of women with diabetes and increased surveillance from 36 weeks' gestation may further lower the number of stillbirths.

**Author contributions** – The article is the original work of all four authors. D. Hall and D. Mason were involved with the design, planning and manuscript writing. J.N. Rossouw was involved with the planning, conduct, data analysis and manuscript writing. G.S. Gebhardt was involved with the planning, data analysis and manuscript editing.

**Conflicts of interest** – None of the authors have any conflicts of interest to declare.

**Acknowledgements** – The authors would like to thank Ms T Esterhuizen and Mr I Karangwa from the Biostatistics Unit, Centre for Evidence-Based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University who assisted with data analysis.

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Received: 14-02-2017 Accepted: 15-05-2017