

Do HbA1c levels during pregnancy predict offspring birthweights in women with pregestational diabetes? A retrospective study

T Hassim* , S Budhram  and DR Hall 

Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa

*Correspondence: tasleemhassim1@gmail.com



Background: Pregestational diabetes poses risks of adverse pregnancy outcomes including macrosomia. Haemoglobin A1c (HbA1c) levels provide information on glycaemia over time.

Objectives: The primary aim was to assess whether sequential HbA1c levels predict macrosomia. Secondary aims included gestational age at delivery.

Design: All women in Tygerberg Academic Hospital with pregestational diabetes, who delivered from January 1, 2022 to June 30, 2024 were included. The Ethics Committee of Stellenbosch University granted approval.

Results: Of the 112 patients, 28% had Type 1 diabetes or LADA, collectively designated Group A. 72% of all patients had Type 2 diabetes or MODY, collectively designated Group B. The proportion of macrosomic babies was 26% in Group A, and 24% in Group B. Amongst macrosomic babies, 50% were born preterm in Group A, and 10% in Group B. In Group B, a low positive correlation was observed between the third trimester HbA1c and the birthweight centile ($p = 0.03$, $r = 0.24$). Furthermore, the difference between the mid- and third trimester HbA1c values showed that the greater the upward difference, the higher the birthweight centile (Group A: $p < 0.01$, $r = 0.51$; Group B $p = 0.01$, $r = 0.28$).

Conclusion: An increasing difference between mid- and third trimester HbA1c values correlated positively with higher birthweight centiles.

Keywords: adverse pregnancy outcomes, fetal macrosomia, HbA1c, pregestational diabetes

Introduction

Diabetes poses a significant public health challenge, both globally and locally. The International Diabetes Federation data published in 2021 estimates that 1 in 10 people 20–79 years of age are living with diabetes.¹ This equates to 537 million people globally. Concerningly, 3 in 4 people with diabetes reside in low- to middle-income countries (LMICs). Twenty-one (21) million live births are affected by hyperglycaemia in pregnancy worldwide, of which four million are from Africa. The number of people living with diabetes in Africa is expected to rise to 33 million by 2030, which equates to an increase of 129%.

While the broad focus of treatment of people living with diabetes is the prevention and management of target-organ damage such as cardiovascular, retinal, and renal disease, pregestational diabetes also poses significant risks during pregnancy and the neonatal period.² These risks include fetal growth acceleration leading to macrosomia, as well as fetal growth restriction (FGR), both of which are associated with an increased incidence of intrauterine demise.³ Macrosomic babies have higher rates of caesarean deliveries and, in the case of vaginal births, higher rates of shoulder dystocia, and birth trauma of the baby and/or mother, in the form of obstetric anal sphincter injury (OASIS).⁴

Multiple studies have investigated how to predict fetal macrosomia in women with diabetes, but there is no consensus to date on the best method. Ultrasound is one such tool, but results are conflicting, and the resource is scarce in some LMICs.⁵ Hyperglycaemia in pregnancy is associated with fetal macrosomia.⁶ Measurement of glycosylated haemoglobin (HbA1c) levels during pregnancy is one of the measures used to monitor glycaemic control over time in women with pre-

existing diabetes, but the physiological changes of pregnancy result in lower HbA1c levels, necessitating pregnancy-specific reference ranges.⁷ HbA1c levels demonstrate a biphasic pattern during pregnancy, with an initial gradual decline to a nadir at 24 weeks' gestation followed by a steady rise to peak near term, as the latter half of normal pregnancy is a state of increased insulin resistance aimed at generating a glucose gradient towards the fetus. Therefore, HbA1c levels during the first trimester, mid-pregnancy, and third trimester may represent different opportunities to predict adverse outcomes in women with pregestational diabetes.⁸ The published data from pregnancies in women with pregestational diabetes demonstrate that higher second- and third-trimester HbA1c levels are associated with adverse pregnancy outcomes, including macrosomia and preterm birth.⁹

This study addresses the limited available data on the HbA1c trends and fetal growth outcomes in women living with pregestational diabetes in South Africa.

Objectives

The primary objective of this study was to investigate whether HbA1c levels (at booking, mid-trimester, or pre-delivery), or the trend of HbA1c levels over the course of pregnancies in women with pregestational diabetes, could be used to predict birthweight. The secondary aims included reporting gestational age at delivery, mode of delivery, and fetal outcomes.

Setting and subjects

A retrospective audit was performed in Tygerberg Academic Hospital, Cape Town, a secondary and tertiary referral centre in South Africa. All women with pregestational diabetes, including overt diabetes first diagnosed in pregnancy, who delivered

during the January 1, 2022–June 30, 2024 period were included. The data were captured in an existing database of women with pregestational diabetes including Type 1 diabetes (T1D) or latent autoimmune diabetes of adults (LADA) (collectively referred to as Group A), or Type 2 diabetes (T2D) or maturity-onset diabetes of the young (MODY) (collectively, Group B). Exclusion criteria included women with a known major haemoglobinopathy or a documented gross fetal anomaly as these characteristics may confound the HbA1c assessment or birthweight. Descriptive maternal and perinatal variables were captured. Where possible, HbA1c values were captured for each trimester of pregnancy. Those patients with missing data were excluded and therefore there were no missing data for the patients included in the data analyses. Macrosomia was defined as a birthweight exceeding 4 000 grams at any gestation.

Design

The data were extracted by the principal investigator from the existing password-protected REDCap database and were de-identified before analysis. Comparisons between continuous measurements, i.e. HbA1c and birthweight, were made using the Pearson correlation coefficient (r). Local charts were used as reference standards to calculate the birthweight centile.¹⁰ The analysis of variance (ANOVA) test was used for comparison between groups. The normality of the data was assessed by inspecting normal probability plots, which were mostly found to be acceptable. Levene's test was used to test for homogeneity of variance, and in all cases found to be not significant, i.e. the data conformed to this assumption. Quantitative variables are expressed as the number/total number n (%), mean \pm SD, or median (interquartile range), according to the distribution of the data. The study authors assessed the association of HbA1c during the first, second, and third trimesters, as well as the trends in the HbA1c values across the trimesters, with offspring birthweight. A p -value < 0.05 was accepted as being statistically significant. The study was approved by the Health Research Ethics Committee of Stellenbosch University,

Faculty of Medicine and Health Sciences (Reference S24/04/088).

Results

During the study period, 20 802 babies with a birthweight ≥ 500 g were delivered in Tygerberg Hospital.⁹ A total of 112 patients were included during the study period, representing 0.5% of the total births at Tygerberg Hospital. Within the study, 31 patients (28%) belonged to Group A (T1D and LADA), and 81 patients (72%) belonged to Group B (T2D and MODY). Pertinent descriptive characteristics are given in Table 1.

Regarding the management of diabetes, 17/81 patients in Group B were noted to be on no treatment for diabetes at the time of booking. These were the cases of overt diabetes diagnosed during pregnancy. These patients were subsequently placed on metformin and/or insulin during pregnancy for blood glucose control. Of the 34/81 patients on oral hypoglycaemic therapy at booking, 3/34 were converted to insulin with discontinuation of oral hypoglycaemic therapy, and 31/34 continued with metformin therapy together with added insulin during pregnancy. Of the 25/81 patients on both oral hypoglycaemic therapy and insulin treatment at booking, 2/25 patients were switched to insulin alone for the course of the pregnancy and 23/25 patients continued with both metformin and insulin treatment for the duration of the pregnancy. There were 5/81 patients on insulin therapy only at booking, of whom 3/5 patients had metformin added during pregnancy. One patient was noted to be on no medication at delivery and one patient continued with insulin alone for the duration of the pregnancy.

One stillbirth was recorded in the Group B cohort. The patient, who had been diagnosed with diabetes around 10 years previously, was receiving oral hypoglycaemic and insulin therapy prior to pregnancy. Her periconception HbA1c was 8.5% and she had poor glycaemic control throughout much of her pregnancy, leading to a switch to insulin analogue therapy. She was hospitalised frequently, and during her admission at 32 weeks for recurrent hypoglycaemia she was diagnosed with placental insufficiency and a large-for-gestational-age (LGA) fetus. Increased fetal surveillance was recommended, but the patient did not adhere to this plan and returned at 35 weeks, when intrauterine fetal death was diagnosed. She subsequently delivered a female fetus weighing 2 885 g.

Sixteen (16) term deliveries were recorded in group A (52%). The median (range) birthweight of these term babies in Group A was 3 625 g (2 525–4 630 g) and the median (range) birthweight centile of these term babies was 91 (16–99.98). Fifty-nine (59) term deliveries were recorded in group B (73%), with a median (range) birthweight of 3 705 g (2 200–4 500 g) and a median (range) birthweight centile of 94.1 (3.28–99.96).

The proportion of macrosomic babies born in group A was 25.8%, with 24.3% born in group B. Of those macrosomic babies born in group A, 50% were preterm at the time of delivery. In group B, only 10% of the macrosomic babies were preterm at the time of delivery. The median gestation-specific HbA1c levels are presented in Table 2.

When testing the booking HbA1c to predict the birthweight centile in Group A, a weak negative correlation was observed ($p = 0.17$, $r = -0.25$). A moderate negative correlation was observed between the mid-trimester HbA1c value and

Table 1: Pertinent descriptive characteristics (data as median/range or n /%)

Factor	Group A ($n = 31$) (28%)	Group B ($n = 81$) (72%)
Age (years)	30 (21–40)	36 (33–45)
Gravidity	3	3
Parity	1	2
Singleton vertex delivery	$n = 6$ (19%)	$n = 20$ (25%)
Elective Caesarean section	$n = 7$ (23%)	$n = 22$ (27%)
Emergency Caesarean section	$n = 18$ (58%)	$n = 39$ (48%)
Average body mass index (BMI) kg/m ² (recorded in 1st trimester)	26 kg/m ² (19–37)	35 kg/m ² (16–58)
Chronic hypertension	$n = 6$ (19%)	$n = 30$ (37%)
Gestational age at delivery (weeks)	37 (33–38)	37 (33–39)
Term deliveries > 37 weeks	$n = 16$ (52%)	$n = 59$ (73%)
Preterm deliveries < 37 weeks	$n = 15$ (48%)	$n = 22$ (27%)
Absolute birthweight mean (SD) non-macrosomic infants	3 042 g (534)	3 164 g (585)
Absolute birthweight mean (SD) macrosomic infants	4 623 g (464)	4 232 g (143)
Shoulder dystocia	$n = 2$ (6%)	$n = 0$
Stillbirths (pregnancy loss > 24 weeks)	0	1

Table 2: Gestation-specific HbA1c (data as median/range or mean/SD)

Factor	Group A	Mean GA (w)	n	Group B	Mean GA (w)	n
Booking HbA1c	9.4% (5.5–14.6)	11 1/7	31	8.4% (5.3–12.9)	12 1/7	81
Mid-trimester HbA1c	8.0% (5.1–14.5)	23 3/7	31	6.9% (5–10.2)	23 0/7	80
Third trimester HbA1c	8.1% (6–12.3)	33 5/7	31	7.1% (5.5–9.5)	33 4/7	80

GA: gestational age.

(w): weeks.

n: number of patients with each HbA1c measurement.

birthweight centile ($p = 0.08$, $r = -0.32$), while no correlation was observed between the third trimester HbA1c value and the birthweight centile; this was not statistically significant ($p = 0.90$, $r = -0.02$).

When assessing Group B, no correlation was found between the booking HbA1c value and the birthweight centile ($p = 0.94$, $r = 0.01$), or between the mid-trimester HbA1c value and the birthweight centile ($p = 0.81$, $r = 0.03$). However, a low positive correlation was observed between the third trimester HbA1c value and the birthweight centile ($p = 0.03$, $r = 0.24$; Figure 1).

Next, trends in the HbA1c values across trimesters were assessed to predict birthweight. In Group A, the difference between the booking and mid-trimester HbA1c values showed no correlation/prediction of the birthweight centile ($p = 0.64$, $r = -0.09$). When examining the difference between the mid- and third trimester HbA1c values, the greater the upward difference, the higher the birthweight centile observed ($p < 0.01$, $r = 0.51$; Figure 2).

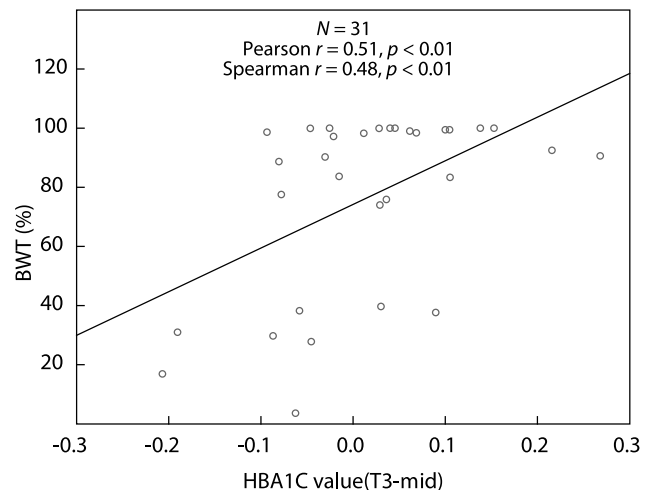
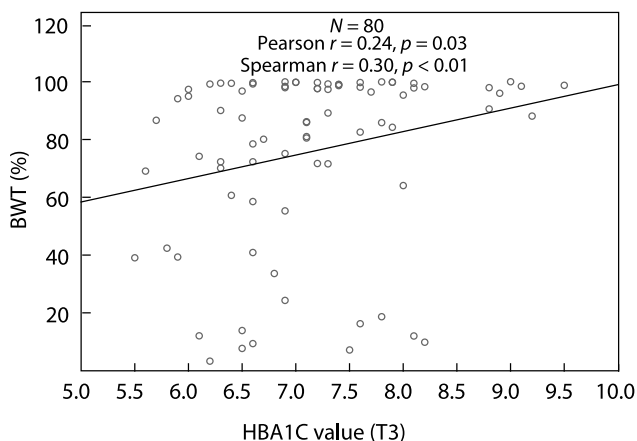
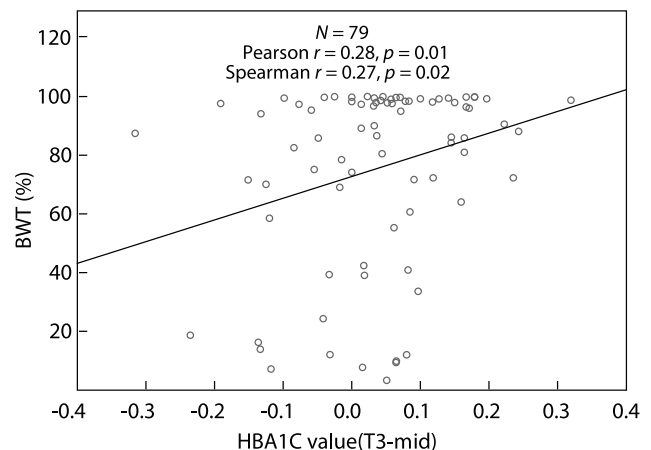
In Group B, the difference between the booking and mid-trimester HbA1c values showed no correlation/prediction of the birthweight centile ($p = 0.79$, $r = 0.03$). When examining the difference between the mid- and third trimester HbA1c values, the greater the upward difference, the higher the birthweight centile observed ($p = 0.01$, $r = 0.28$; Figure 3).

Furthermore, the relationship between the HbA1c value for each trimester and an absolute birthweight of $> 4\,000$ g was tested. In Group A, 23 babies were born weighing $< 4\,000$ g mean and 8 babies were born weighing $> 4\,000$ g. The mean booking HbA1c values showed no significant difference (9.6% SD [2.1] vs. 8.9% SD [1.0]; $p = 0.42$), nor did the mean HbA1c mid-trimester values (8.1% SD [2.0] vs. 7.9% SD [0.8]; $p = 0.76$).

Again, in the third trimester, the mean HbA1c values were comparable (8.0% SD [1.7] vs. 8.3% SD [1.1]; $p = 0.65$).

In Group B, 61 babies were born weighing $< 4\,000$ g and 20 babies were born weighing $> 4\,000$ g. The mean booking HbA1c values showed no significant difference (8.6% SD [1.6] vs. 8.1% SD [1.4]; $p = 0.24$), nor did the mean HbA1c mid-trimester value (6.9% SD [1.1] vs. 6.7% SD [0.7]; $p = 0.52$). Again, in the third trimester, the mean HbA1c values were comparable (7.1% SD [0.9] vs. 7.2% SD [0.8]; $p = 0.56$).

Lastly, the trend of the HbA1c values across trimesters and the correlation with a birthweight $> 4\,000$ g was examined. In Group A, the mean difference in booking and mid-trimester

**Figure 2:** Group A: difference between mid- and third trimester HbA1c values vs. birthweight (BWT) centile.**Figure 1:** Group B: third trimester HbA1c value vs. birthweight (BWT) centile.**Figure 3:** Group B: difference between mid- and third trimester HbA1c values vs. birthweight (BWT) centile.

values showed no difference for babies weighing $< 4\,000\text{ g}$ or $> 4\,000\text{ g}$ ($p = 0.48$). The same applied to the mean difference in mid-trimester and third trimester values ($p = 0.23$). In Group B, both of the above-mentioned differences were non-significant, being $p = 0.31$ and $p = 0.16$, respectively.

Discussion

This study was undertaken to assess the relationship between glycaemic control, as assessed by HbA1c levels during pregnancy, and birthweight among women with pregestational diabetes. The main finding was that an increasing difference between the mid- and third trimester HbA1c values correlated positively with higher birthweight centiles.

We have clearly demonstrated, in our cohort, a relationship between increasing HbA1c values during the second and third trimester and neonatal outcomes including, most importantly, fetal macrosomia. When examining the trend for HbA1c values, we found a linear relationship between HbA1c values and birthweight centile. The third trimester seems to be associated with increasing birthweight centile and macrosomia, suggesting that measures should be put in place to stabilise or improve glucose control in the second and third trimester to reduce the incidence of fetal macrosomia. Additionally, we found that mean HbA1c values across both groups in the first and second trimester was higher in babies weighing $< 4\,000\text{ g}$. However further research is needed to establish whether these babies were appropriately grown or growth restricted. Conversely, in the third trimester, the mean HbA1c was higher among babies born weighing $> 4\,000\text{ g}$, suggesting that improving control in the mid-third trimester would reduce the risk of fetal macrosomia and associated complications.

Only 51% of the babies born in Group A were delivered after 37 weeks' gestation, compared with 72% in Group B. The birthweight centiles and macrosomia rate remained similar in both groups. Interestingly, 50% of macrosomic fetuses were born preterm in group A, compared with only 10% in Group B. This highlights the importance of increased fetal surveillance of women living with T1D. Correct patient selection for delivery earlier than 38 weeks, as recommended in the UK's National Institute for Health and Care Excellence (NICE) guidelines, remains challenging, especially in our resource-limited setting where neonatal morbidity concerns are related to hyaline membrane disease.

The association between HbA1c levels and adverse pregnancy outcomes has been reported in previous studies. Among these studies, the landmark Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study has provided the most convincing data.¹¹ Measurement of HbA1c levels as a biomarker is an attractive option as it provides an integrated view of glycaemia over a certain period. Current practice and guidelines recommend that HbA1c levels be measured at monthly intervals at a minimum.¹² Such a practice would place an additional burden on an already resource-constrained setting. There is evidence supporting less frequent HbA1c monitoring in diabetic pregnancies. The NICE guidelines currently advise a target HbA1c of less than 6.1% pre-conception.¹³ Concerningly, the median HbA1c values at booking in both groups were far higher than this, with a median booking HbA1c of 9.3% for Group A, and 8.5% for Group B. This highlights the need to improve access to pre-conception counselling to reduce the risk of adverse pregnancy outcomes. However, this is particularly difficult, as most pregnancies in South Africa are probably unplanned.

Multiple studies have looked at how best to predict macrosomia in the offspring of women living with diabetes, but there has been no consensus on the ideal or best method to date.⁵ Ultrasound is one such tool, but results are conflicting, and machines and trained personnel are not always available in LMICs. A systematic review and meta-analysis by Farrar et al.,¹⁴ which included 207 172 women, examined the correlation between maternal glycaemic levels and adverse pregnancy outcomes in women with gestational and pregestational diabetes, to determine thresholds for identifying those at risk of adverse perinatal outcomes.¹⁴ The review demonstrated a consistent graded linear association between glycaemic levels and perinatal outcomes, including Caesarean section, induction of labour, LGA babies, macrosomia, and shoulder dystocia. There is currently no research from sub-Saharan Africa looking at the correlation between glycaemic levels and perinatal outcomes.

Pregestational diabetes is the main risk factor for diabetic fetopathy.¹⁵ Diabetic fetopathy is a severe complication, defined as systematic changes in newborns that can be caused by maternal pre-existing or gestational diabetes. The affected newborn may suffer respiratory distress after birth and obesity or metabolic syndrome later in life. The growing population of young persons with metabolic syndrome raises great concern regarding cardiovascular disease developing as early as adolescence, also known as Barker's hypothesis. The most common sign of diabetic fetopathy is fetal macrosomia. Studies have shown a risk of up to 45% of macrosomia in infants born from diabetic mothers, which is a three times higher risk than the rate in the normoglycaemic population.¹⁶ Due to impaired maternal glycaemic control combined with increasing insulin resistance, an increased level of glucose may result in excess glucose crossing the placental barrier, contrary to insulin. In the second trimester, the fetal pancreas is mature enough to secrete insulin. Due to the combination of maternal hyperglycaemia, fetal hyperglycaemia, and subsequent fetal hyperinsulinemia, fetal adipose production increases.

Among pregnant women with diabetes, fetal macrosomia is associated with an increased risk of stillbirth.³ Only one stillbirth (0.89%) was recorded during the 30-month study. Although our study was much shorter, it differs from the available data for South Africa. Huddle published an 11-year audit of outcomes of diabetic women in Soweto, where he noted 3.9% and 1.8% stillbirths in women with T1D and T2D, respectively.¹⁷ A publication by Hall et al.¹⁸ from Tygerberg Hospital found no stillbirths among women living with T1D, and 6.5% among women living with T2D. The most recent audit published by Rossouw et al.,¹⁹ looking at stillbirths amongst women with diabetes in Tygerberg Hospital, noted that stillbirths attributed to diabetes contributed to 2.3% of the stillbirths recorded during the study period, 28% of which occurred in women with T1D and 64% in women with T2D. The finding of improved outcomes in our cohort could be explained by stricter management of all patients where target glucose levels were not maintained. This is further evidenced by the finding that 92% of Type 2 diabetics were treated with both metformin and insulin to maintain glucose control. These results are strikingly different from the metformin success rate of 79% rate published by Silva et al.²⁰

Our study sheds light on the relationship between glycaemic control in the third trimester of pregnancy, as reflected by the HbA1c value, and macrosomic babies. The strengths of the

study include the addition of HbA1c trends and birthweight centiles, as well as the use of the local South African cohort in the sample population. The modest size of the study as well as its retrospective nature, which limits the strength of the findings, is acknowledged. Missing data resulted in the exclusion of patients from the study cohort. In addition, the influence of hypertensive disease on birthweight was not captured in this study. We did not control for confounders, such as gestational weight gain, but we do appreciate that there are many factors that contribute to birthweight. We recognise the limitation of diagnosing FGR in the diabetic population as expected fetal weight is generally higher than that of a non-diabetic pregnancy. It is hoped that this work will stimulate further research on both extremes of fetal growth in pregnancies with diabetes, and measures to improve outcomes.

Conclusion

The current study has shown a continuous relationship between increasing HbA1c values in the second and third trimester and fetal macrosomia, in women living with pregestational diabetes.

Acknowledgements – The authors would like to thank Prof. Martin Kidd from the Biostatistics Unit, Centre for Evidence-Based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, who assisted with data analysis. The authors acknowledge the dedication and assistance of the medical and nursing personnel in the Obstetric Special Care Unit, as well as the multidisciplinary team in the management of pregestational diabetic patients at Tygerberg Hospital.

Disclosure statement – No potential conflict of interest was reported by the author(s).

Funding – The author(s) reported there is no funding associated with the work featured in this article.

ORCID

T Hassim  <http://orcid.org/0009-0007-3939-4990>

S Budhram  <http://orcid.org/0000-0002-5747-1714>

DR Hall  <http://orcid.org/0000-0002-2344-3969>

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Received: 6-04-2025 Accepted: 9-10-2025