

Glycemic control and pregnancy outcomes in patients with diabetes in pregnancy: A retrospective study

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ABSTRACT

Context: Diabetes in pregnancy (DIP) is either pregestational or gestational. **Aims:** To determine the relationship between glycemic control and pregnancy outcomes in a cohort of DIP patients. **Settings and Design:** In this 12-month retrospective study, a total of 325 Saudi women with DIP who attended the outpatient clinics at a tertiary center Riyadh, Saudi Arabia, were included. **Subjects and Methods:** The patients were divided into two groups, those with glycated hemoglobin (HbA1c) $\leq 6.5\%$ (48 mmol/mol) and those with glycated hemoglobin (HbA1c) above 6.5%. The two groups were compared for differences in maternal and fetal outcomes. **Statistical Analysis Used:** Independent Student's *t*-test and analysis of variance were performed for comparison of continuous variables and Chi-square test for frequencies. Odds ratio and 95% confidence intervals were calculated using logistic regression. **Results:** Patients with higher HbA1c were older ($P = 0.0077$), had significantly higher blood pressure, proteinuria ($P < 0.0001$), and were multiparous ($P = 0.0269$). They had significantly shorter gestational periods ($P = 0.0002$), more preterm labor ($P < 0.0001$), more perineal tears ($P = 0.0406$), more miscarriages ($P < 0.0001$), and more operative deliveries ($P < 0.0001$). Their babies were significantly of greater weight, had more Neonatal Intensive Care Unit (NICU) admissions, hypoglycemia, and macrosomia. **Conclusions:** Poor glycemic control during pregnancy is associated with adverse maternal and fetal outcomes (shortened gestational period, greater risk of miscarriage, increased likelihood of operative delivery, hypoglycemia, macrosomia, and increased NICU admission). Especially at risk are those with preexisting diabetes, who would benefit from earlier diabetes consultation and tighter glycemic control before conception.

Key words: Diabetes in pregnancy, gestational diabetes, pregnancy adverse outcomes, Type 1 diabetes, Type 2 diabetes

INTRODUCTION

Diabetes in pregnancy (DIP) is either pregestational or gestational diabetes mellitus (GDM). Occasionally, Type 1 DM (T1DM) is diagnosed during pregnancy.^[1,2]

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DM^[3] and GDM are common in Saudi Arabia. One study found that 12.5% of the randomly recruited pregnant Saudis attending the clinic in Jeddah had GDM.^[4] A larger prospective study in Riyadh found that 8.6% pregnant women had GDM.^[5] Risk factors for GDM include a personal history of impaired glucose tolerance, GDM, or a newborn weighing >4 kg (macrosomia) in an earlier pregnancy. Other risk factors include advancing maternal age, maternal obesity, increased susceptibility in Arabs,^[6] and

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a family history of T2DM. Similar to the pathophysiology of T2DM, GDM is associated with insulin resistance and relative insulin deficiency.^[7] Glycemic control is essential in pregnant patients with DIP since even minor degrees of hyperglycemia have adverse effects on the mother and fetus.^[8] Despite the high prevalence of DIP in Saudis, there is a paucity of data about the relationship between glycemic control during pregnancy and maternal and fetal outcomes. This study aims to determine the impact of glycemic control during pregnancy on maternal and fetal outcomes in a cohort of patients with DIP.

SUBJECTS AND METHODS

Study population

In this 12-month retrospective study, 325 pregnant women attending the DIP clinics at a tertiary center in Riyadh, Saudi Arabia, from May 2012 to April 2013 were identified. These women were monitored for maternal and fetal complications during pregnancy from their first prenatal visit until 6 weeks postpartum. Institutional Ethical Committee clearance was obtained. A total of 334 DIP patients were initially identified; however, during data collection, six patients were lost to follow-up and three patients opted for delivery at another hospital.

Criteria for diagnosis of gestational diabetes mellitus

The diagnosis of GDM was in accordance with the World Health Organization guidelines^[9] at 26–28 weeks of gestation or earlier in high-risk patients such as those with a previous GDM or glucose intolerance using the Siemens Dimension RxL Max Integrated Chemistry System. The glycated hemoglobin (HbA1c) reference values were 4.5–6.2% (25.7–44.3 mmol/mol).

Management

- Self-monitoring of blood glucose (SMBG) at home, aiming for fasting blood glucose of ≤ 5.3 mmol/L (≤ 95 mg/dl), and a 2-h postprandial level of ≤ 7.0 mmol/L (≤ 126 mg/dl)^[10,11]
- Medical nutrition therapy (MNT) with Vitamin D and probiotics supplements (studies support this beneficial relationship)^[12,13]
- Walking for 30 min/day
- Ophthalmology referral for patients with preexisting diabetes
- Patients with preexisting diabetes, we recommended basal-bolus insulin regimen and suggested continuous subcutaneous insulin infusion (insulin pump) if target was not achieved
- GDM patients failing to meet target SMBG levels on MNT were commenced on insulin therapy as follows:

- Fasting hyperglycemia – single dose of neutral protamine Hagedorn insulin or detemir (evening)
- Postprandial hyperglycemia (without fasting hyperglycemia) – either regular human insulin or rapid-acting analog (aspart/lispro) before each meal
- Fasting and postprandial hyperglycemia – basal-bolus insulin regimen.

At the first prenatal checkup, patient demographic data, prepregnancy body mass index (BMI), parity, family history of diabetes, baseline HbA1c, and subtype of DIP were documented. Patients were seen at 1–4 weekly intervals and the following information was collected.

- HbA1c level
- SMBG data
- Details of any insulin regimen
- Blood pressure (BP).

Patients with acceptable-controlled diabetes (HbA1c $\leq 6.5\%$) were seen monthly until 30 weeks gestation, then at 1–2 weekly intervals until delivery. Poorly controlled patients (HbA1c $> 6.5\%$) were seen at 1–2 weekly intervals. Intravenous insulin was administered during labor to patients with preexisting diabetes with glucose levels above 4–7 mmol/L.^[14]

Other variables studied

Pregnancy outcomes were noted (miscarriage or delivery), and for those proceeding to delivery, duration of gestation and methods of delivery normal spontaneous vaginal delivery (NSVD included normal vaginal and assisted vaginal) or cesarean section (CS) were documented. Perineal tears, polyhydramnios, hypertension, proteinuria, preeclampsia, and preterm labor were documented. Neonatal data such as birth status (live or intrauterine fetal death [IUFD]), weight, macrosomia, gender, hypoglycemia, hyperbilirubinemia, Apgar score and any congenital anomaly were noted. Postnatal complications such as Neonatal Intensive Care Unit (NICU) admissions and neonatal mortality were documented.

Statistical methods

Data were presented as percentage (%) for frequencies and mean and standard deviation for continuous variables. Independent Student's *t*-test and analysis of variance were done for comparison of continuous variables and Chi-square test for frequencies. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated using logistic regression. A $P \leq 0.05$ was considered statistically significant.

RESULTS

Characteristics of study population

Of the 325 DIP patients, 54.46% ($n = 177$) had GDM, 29.23% ($n = 95$) had T2DM, and 16.31% ($n = 53$) had T1DM. The patients' age ranged from 19 to 55 years (mean 33.43 ± 6.632 years). The mean gestational period for the whole group was 37.53 ± 2.49 weeks. The total number of live births was 276/325 (84.92%), with a mean gestational period of 37.59 ± 2.4 weeks. The remaining 36/325 (11.08%) patients had a miscarriage at 11.24 ± 3.64 weeks. There were 13/325 (4.0%) IUFDs at 39.83 ± 2.4 weeks. A total of 286 newborns comprising 269 singleton births, five sets of twins, one set of triplets, and one set of quads were included in this study.

Characteristics based on glycated hemoglobin value

Patients were divided into two groups based on the mean HbA1c value (mean of all HbA1c readings got from each patient from baseline reading up to last prenatal visit). Group 1 had patients with HbA1c $\leq 6.5\%$ (Group 1, $n = 126$) and Group 2 had patients with HbA1c $> 6.5\%$ (Group 2, $n = 199$). The characteristics and the significant differences between the two groups are shown in Table 1. The respective number of patients with GDM, T2DM, and T1DM in Group 1 was 94/126 (74.6%), 23/126 (18.3%), and 9/126 (7.1%), respectively. The respective numbers in Group 2 were 83/199 (41.7%), 72/199 (36.2%), and 44/199 (22.1%). Compared to patients in Group 1, patients in Group 2 were significantly older (33.563 years vs.

31.6 years; $P = 0.0077$), significantly had higher BP readings, and significantly more likely to be administered insulin (84.5% vs. 58.9%; $P < 0.0001$). Group 2 patients had significantly more risk of having miscarriages (16.5% vs. 2.3%; $P < 0.0001$), significantly shorter gestational period (37.018 weeks vs. 38.122 weeks; $P = 0.0002$), and more likely to have operative deliveries (70.5% vs. 40.7%; $P < 0.0001$), showing that there is greater risk if there is poor glycemic control. They also had significantly more likelihood of having proteinuria (62% vs. 26%; $P < 0.0001$).

Group 2 babies weighed significantly more (3.425 kg vs. 3.1729 kg; $P = 0.0006$) and had significantly more hypoglycemia and macrosomia (both $P < 0.0001$) [Table 2]. Figure 1 shows the significant differences between both groups. For better comparison in each type of diabetes, the patients were divided into two groups, HbA1c $\leq 6.5\%$ (Group 1) and HbA1c $> 6.5\%$ (Group 2).

Gestational diabetes mellitus patients

There were 177 patients with GDM, of which 94 patients with HbA1c $\leq 6.5\%$ (Group 1) and 83 patients with HbA1c $> 6.5\%$ (Group 2). There were 3 and 10 miscarriages in the respective group. There were 5 and 1 multiple pregnancies in the respective group. Total full-term single pregnancy was 86 in Group 1 and 72 in Group 2. There was one stillbirth in each group so that babies studied were 85 in Group 1 and 71 in Group 2. The characteristics of the two groups are shown in Table 3. Patients in Group 2 were significantly older, had significantly higher

Table 1: Characteristics of the study participants grouped on basis of mean glycated hemoglobin values

Characteristics/outcomes	HbA1c $\leq 6.5\%$ ($n=126$)	HbA1c $> 6.5\%$ ($n=199$)	P
Maternal characteristics, mean (SD)			
Age (years)	31.60 (5.75)	33.563 (6.79)	0.0077
Prepregnancy BMI	30.84 (5.63)	31.71 (5.71)	0.18
Mean systolic BP [§]	114.67 (16.3)	119.40 (12.8)	0.0040
Mean diastolic BP [§]	69.484 (9.58)	72.234 (10.3)	0.016
Mean blood glucose (mg/dl)	124.98 (10.1)	177.46 (33.5)	<0.0001
Mean HbA1c [¶] (%)	5.9575 (0.35)	7.7818 (1.11)	<0.0001
Family history of DM, number of patients (%)	86 (68.25)	151 (75.87)	0.1586
Multiparous [‡]	77 (61.11)	146 (73.37)	0.0269
Insulin use (T2DM and GDM)	69 (58.9)	131 (84.5)	<0.0001
Multiple pregnancy	5 (4.13)	2 (1.29)	0.2460
Obstetrical outcomes, number of patients (%)			
NSVD	73 (59.3)	49 (29.5)	<0.0001
CS	50 (40.7)	117 (70.5)	
Miscarriages [¶]	3 (2.3)	33 (16.5)	<0.0001
Preterm labor <35 weeks (only singleton pregnancies)	1 (0.86)	25 (15.2)	<0.0001
Polyhydramnios [†]	4 (3.2)	19 (11.4)	0.0146
Hypertension	9 (7.3)	26 (15.6)	0.0444
Proteinuria	32 (26)	103 (62)	<0.0001
Preeclampsia	2 (1.7)	4 (2.4)	1.0000

[§]Mean HbA1c was defined as mean value of all the HbA1c readings got from each patient from baseline reading up to last prenatal visit, [¶]Mean blood pressure was defined as mean readings of blood pressure collected from the patient from the first clinic visit up to time before delivery, [‡]Multiparous means > 2 deliveries, [†]Polyhydramnios was defined as when the volume of amniotic fluid exceeds the norm for the gestational age which is diagnosed by ultrasound, [¶]Miscarriage includes missed miscarriage, inevitable miscarriage, complete or incomplete miscarriage and threatened miscarriage, ectopic and molar pregnancy. DM: Diabetes mellitus, GDM: Gestational diabetes mellitus, HbA1c: Glycated hemoglobin, NSVD: Normal spontaneous vaginal delivery included normal vaginal and assisted vaginal, CS: Cesarean section, SD: Standard deviation

Table 2: Characteristics of the newborn grouped on basis of mean glycated hemoglobin values

Characteristics/outcomes	HbA1c ≤6.5% (n=126)	HbA1c >6.5% (n=199)	P
Newborn characteristics, mean (SD) (n)			
Gestational age at delivery (weeks)	38.122 (2.0) (118)	37.018 (2.74) (164)	0.0002
Birth weight (kg)	3.1729 (0.511) (116)	3.4250 (.629) (153)	0.0006
Apgar scores at 10 min	9.5299 (0.915) (116)	9.1961 (0.939) (153)	0.0037
Newborn outcomes, number of patients (%)			
IUFD/stillbirth	2 (1.6)	11 (6.7)	0.0455
Premature delivery <37 weeks gestation	16 (13.5)	43 (26.2)	0.0049
Macrosomia	10 (8.4)	41 (25)	<0.0001
Shoulder dystocia	0 (0)	2 (1.2)	0.5238
Perineal tear	3 (2.5)	14 (8.5)	0.0406
NICU ^a admission	7 (5.9)	28 (17)	0.0032
Hypoglycemia	7 (6)	46 (30)	<0.0001
Hyperbilirubinemia	3 (2.3)	8 (4)	0.5391
Congenital anomaly	2 (1.6)	7 (4.2)	0.3076

^aNICU: Neonatal Intensive Care Unit was defined by admission to any type of unit for care more intensive than normal newborn care. SD: Standard deviation, IUFD: Intrauterine fetal death, HbA1c: Glycated hemoglobin

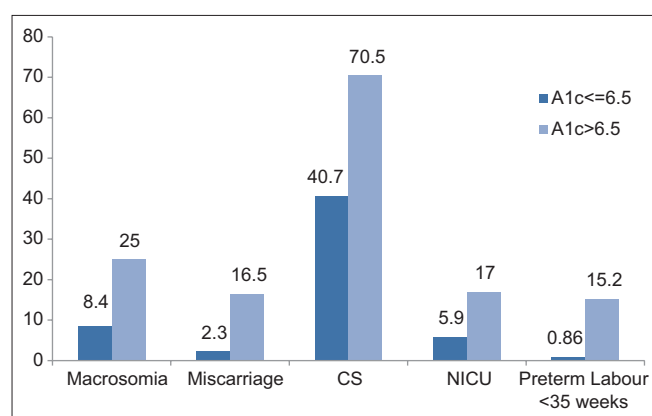


Figure 1: Significant differences found between groups with glycated hemoglobin ≤6.5% and those with glycated hemoglobin >6.5% in gestational diabetes mellitus patients. Macrosomia, miscarriage, CS: Cesarean section, NICU: Neonatal Intensive Care Unit, Admissions and preterm labor <35 weeks are in shown as percentages

prepregnancy BMI, and had higher mean blood sugar compared to their GDM counterparts who had lower HbA1c values. Patients in Group 2 also had a significantly higher rate of having a family history of diabetes. They had significantly high parity, higher cesarean rates (59% vs. 41.76%; $P = 0.0408$), and lower NSVD rates; they were significantly more likely to receive insulin therapy (72.28% vs. 52.12%; $P = 0.0052$). Group 2 patients had significantly more risk of having miscarriages (12% vs. 3.19%; $P = 0.04$ OR 4.155 [95% CI 1.003–19.836]), showing that there is greater risk if there is poor glycemic control. They had significantly shorter gestational period (37.5 weeks vs. 38.26 weeks; $P < 0.0268$), significantly lower Apgar scores, and significantly more likely to go into preterm delivery. During delivery, the GDM patients with higher HbA1c values had significantly greater rates of perineal tears. The neonates of Group 2 had significantly greater NICU admissions (15.492% vs. 4.7%; $P = 0.029$) and higher

rates of macrosomia (35.21% vs. 7.058%; $P < 0.0001$) and hypoglycemia [Table 4].

Type 2 diabetes mellitus patients

There were 95 patients with T2DM, of which 23 patients with HbA1c ≤6.5% (Group 1) and 72 patients with HbA1c >6.5% (Group 2). There were no miscarriages or multiple pregnancies in Group 1 and 16 miscarriages and one multiple pregnancy in Group 2. Total full-term single pregnancy was 23 in Group 1 and 55 in Group 2. There was one and four stillbirths in each respective group, so babies studied were 22 in Group 1 and 51 in Group 2. The characteristics of the two groups are shown in Table 5. Patients in Group 2 had significantly higher mean blood sugar compared to their T2DM counterparts who had lower HbA1c values. Significantly, more patients in Group 2 had a family history of diabetes. They had significantly high parity, significantly more likely to receive insulin therapy, significantly shorter gestational period (36.5 weeks vs. 38.04 weeks; $P < 0.0304$), significantly lower Apgar scores, and significantly more likely to go into preterm delivery with a significant increase in proteinuria. Group 2 patients were more likely to have operative deliveries (78.57% vs. 34.78%; $P = 0.0005$), showing that there is greater risk if there is poor glycemic control. Group 2 patients had significantly more risk of having miscarriages (22.2% vs. 0%; $P = 0.01$ OR infinity [95% CI 1.187-infinity]). There were more NICU admissions, macrosomia, and hypoglycemia in the neonates of Group 2 compared to Group 1 neonates [Table 6].

Type 1 diabetes mellitus patients

There were 53 patients with T1DM, of which nine patients with HbA1c ≤6.5% (Group 1) and 44 patients with HbA1c >6.5% (Group 2). There were no miscarriages or multiple pregnancies in Group 1 and seven miscarriages and no multiple pregnancies in Group 2. Total full-term

Table 3: Characteristics of the gestational diabetes mellitus study participants

Characteristics/outcomes	HbA1c ≤6.5% (n=94)	HbA1c >6.5% (n=83)	P
Maternal characteristics, mean (SD)			
Age (years)	30.63 (5.45)	33.3 (6.38)	0.0026
Prepregnancy BMI	30.495 (5.443)	32.242 (5.667)	0.0394
Mean systolic BP ^a	114.17 (13.22)	117.32 (13.26)	0.1182
Mean diastolic BP ^a	68.62 (9.44)	69.62 (10.16)	0.5008
Mean blood glucose (mg/dl)	124.9 (9.24)	163.12 (23.8)	<0.0001
Mean HbA1c ^c (%)	5.9553 (0.3222)	7.2986 (0.821)	<0.0001
Family history of DM, number of patients (%)	71 (75.53)	73 (87.95)	0.0302
Multiparous ^x	55 (58.51)	61 (73.49)	0.0379
Insulin use (T2DM and GDM)	49 (52.12)	60 (72.28)	0.0052
Multiple pregnancy	5 (5.32)	1 (1.23)	0.2185
Obstetrical outcomes number of patients (%)			
NSVD	53 (58.24)	30 (41)	0.0408
CS	38 (41.76)	43 (59)	
Miscarriages ^o	3 (3.19)	10 (12)	0.0400
Preterm labor <35 weeks (only singleton pregnancies)	1 (1.176)	6 (8.45)	0.0500
Polyhydramnios [†]	3 (3.529)	6 (8.45)	0.3057
Hypertension	4 (4.70)	6 (8.45)	0.5167
Proteinuria	17 (20)	24 (33.8)	0.0769
Preeclampsia	2 (2.352)	3 (4.225)	0.6636

^aMean HbA1c was defined as mean value of all the HbA1c readings got from each patient from baseline reading up to last prenatal visit, ^bMean blood pressure was defined as mean readings of blood pressure collected from the patient from the first clinic visit up to time before delivery, ^cMultiparous means >2 deliveries, [†]Polyhydramnios was defined as when the volume of amniotic fluid exceeds the norm for the gestational age which is diagnosed by ultrasound, ^oMiscarriage includes missed miscarriage, inevitable miscarriage, complete or incomplete miscarriage and threatened miscarriage, ectopic and molar pregnancy. DM: Diabetes mellitus, GDM: Gestational diabetes mellitus, HbA1c: Glycated hemoglobin, NSVD: Normal spontaneous vaginal delivery included normal vaginal and assisted vaginal, CS: Cesarean section, SD: Standard deviation

Table 4: Characteristics of the newborn born to gestational diabetes mellitus mothers

Characteristics/outcomes	HbA1c ≤6.5% (n=94)	HbA1c >6.5% (n=83)	P
Newborn characteristics, mean (SD) (n)			
Gestational age at delivery (weeks)	38.26 (1.93) (86)	37.5 (2.39) (72)	0.0268
Birth weight (kg)	3.1652 (0.5092) (85)	3.4591 (0.7558) (71)	0.0043
Apgar scores at 10 min	9.6 (0.79) (85)	9.39 (0.78) (71)	0.0968
Newborn outcomes, number of patients (%)			
IUFD/stillbirth	1 (1.176)	1 (1.23)	1
Premature delivery <37 weeks gestation	13 (15.294)	15 (21.12)	0.4044
Macrosomia	6 (7.058)	25 (35.21)	<0.0001
Shoulder dystocia	0 (0)	1 (1.23)	0.4551
perineal tear	1 (1.176)	6 (8.45)	0.0473
NICU ^o admission	4 (4.7)	11 (15.492)	0.0292
Hypoglycemia	4 (4.7)	11 (15.4)	0.0292
Hyperbilirubinemia	1 (1.176)	2 (2.46)	0.5916
Congenital anomaly	2 (2.352)	4 (5.633)	0.4121

^oNICU: Neonatal Intensive Care Unit was defined by admission to any type of unit for care more intensive than normal newborn care. SD: Standard deviation, IUFD: Intrauterine fetal death, HbA1c: Glycated hemoglobin

single pregnancy was nine in Group 1 and 37 in Group 2. There were no stillbirths in Group 1 and six in Group 2, so babies studied were nine in Group 1 and 31 in Group 2. The characteristics of the two groups are shown in Table 7. Patients with Group 2 had significantly higher mean blood sugar compared to their T1DM counterparts who had lower HbA1c values. They had significantly shorter gestational period (36.84 weeks vs. 38.78 weeks; $P = 0.0327$) and significantly more likely to go into preterm delivery. Group 2 patients were more likely to have operative deliveries (68.18% vs. 44.44%; $P = 0.0388$), showing that there is greater risk if there is poor glycemic control. Group 2 patients had significantly more risk of having miscarriages (19% vs. 0%; $P = 0.0491$). The neonates of

Group 2 had significantly more hypoglycemia compared to neonates of Group 1 [Table 8].

Factors influencing maternal and fetal outcomes

Table 9 shows which factors influenced the likelihood of some maternal and fetal outcomes. GDM patients with higher HbA1c values had twice as much chance of having a CS and almost four times more likelihood of miscarriage and NICU admission and seven times more increased odds of having macrosomia than if their HbA1c was controlled. Having a higher HbA1c in T2DM increased the risk of CS by seven times and a high increase in odds of miscarriage compared to T2DM who had controlled HbA1c values. T1DM patients had very high five times more odds for

Table 5: Characteristics of the participants who had Type 2 diabetes mellitus

Characteristics/outcomes	HbA1c ≤6.5% (n=23)	HbA1c >6.5% (n=72)	P
Maternal characteristics, mean (SD)			
Age (years)	35.74 (4.4)	36.76 (5.65)	0.4288
Prepregnancy BMI	33.822 (5.784)	33.044 (5.175)	0.5438
Mean systolic BP ^a	115.48 (27.19)	120.49 (11.81)	0.2157
Mean diastolic BP ^a	71.13 (9.77)	72.08 (11.02)	0.7118
Mean blood glucose (mg/dl)	124 (13.32)	185.19 (38.08)	<0.0001
Mean HbA1c ^c (%)	5.9196 (0.456)	8.0271 (1.2094)	<0.0001
Duration of DM in years	4.478 (3.812)	5.283 (4.128)	0.4093
Family history of DM, number of patients (%)	13 (56.52)	64 (88.89)	0.0449
Multiparous ^b , number of patients (%)	18 (78.26)	68 (94.44)	0.0351
Insulin use as therapy, number of patients (%)	20 (86.95)	71 (98.61)	0.0428
Multiple pregnancy, number of patients (%)	0 (0)	1 (1.923)	1
Obstetrical outcomes, number of patients (%)			
NSVD	15 (65.22)	12 (21.43)	0.0005
CS	8 (34.78)	44 (78.57)	
Miscarriages ^d	0 (0)	16 (22.22)	0.0100
Preterm labor <35 weeks (only singleton pregnancies)	1 (4.545)	8 (15.68)	0.2618
Polyhydramnios ^e	1 (4.34)	1 (1.38)	0.4314
Hypertension	5 (2.173)	16 (2.191)	1
Proteinuria	13 (56.52)	64 (87.67)	0.0008
Preeclampsia	0 (0)	0 (0)	-

^aMean HbA1c was defined as mean value of all the HbA1c readings got from each patient from baseline reading up to last prenatal visit, ^bMean blood pressure was defined as mean readings of blood pressure collected from the patient from the first clinic visit up to time before delivery, ^cMultiparous means >2 deliveries, ^dPolyhydramnios was defined as when the volume of amniotic fluid exceeds the norm for the gestational age which is diagnosed by ultrasound, ^eMiscarriage includes missed miscarriage, inevitable miscarriage, complete or incomplete miscarriage and threatened miscarriage, ectopic and molar pregnancy. DM: Diabetes mellitus, HbA1c: Glycated hemoglobin, NSVD: Normal spontaneous vaginal delivery included normal vaginal and assisted vaginal, CS: Cesarean section, SD: Standard deviation

Table 6: Characteristics of the newborn born to Type 2 diabetes mellitus mothers

Characteristics/outcomes	HbA1c ≤6.5% (n=23)	HbA1c >6.5% (n=72)	P
Newborn characteristics, mean (SD) (n)			
Gestational age at delivery (weeks)	38.04 (1.33) (23)	36.5 (3.24) (55)	0.0304
Birth weight (kg)	3.176 (.5223) (22)	3.201 (.8548) (51)	0.8983
Apgar scores at 10 min	9.5 (0.91) (22)	8.92 (1.15) (51)	0.0397
Newborn outcomes, number of patients (%)			
IUFD/stillbirth	1 (4.34)	4 (7.69)	1
Premature delivery <37 weeks gestation	2 (9.09)	17 (33.33)	0.0413
Macrosomia	3 (13.63)	10 (19.6)	0.7420
Shoulder dystocia	0 (0)	1 (1.96)	1
perineal tear	2 (9.09)	4 (7.84)	1
NICU ^a admission	2 (9.09)	11 (21.568)	0.3195
Hypoglycemia	2 (9)	17 (33.3)	0.0413
Hyperbilirubinemia	1 (4.5)	2 (3.9)	1
Congenital anomaly	0 (0)	1 (1.96)	1

^aNICU: Neonatal Intensive Care Unit was defined by admission to any type of unit for care more intensive than normal newborn care. SD: Standard deviation, IUFD: Intrauterine fetal death, HbA1c: Glycated hemoglobin

CS compared to the T1DM who had better glycemic control. Overall, when HbA1c increased patients had an almost 4-fold increased likelihood of having a CS, NICU admission and macrosomia babies and almost eight times increased likelihood of miscarriage compared to patients who had controlled HbA1c values.

DISCUSSION

GDM normally accounts for 88% of DIP, T2DM patients comprise 8%, and T1DM patients make up the remaining 4%.^[15-17] This discrepancy from the norm in this population is due to the fact that this study was done

in the outpatient clinics at a tertiary referral center where most patients were referred T1DM and T2DM cases from other places. Poor glycemic control during pregnancy is associated with adverse maternal and fetal outcomes.^[18-20] Risks to the women with DIP that was seen in this study include miscarriage, operative delivery, and preterm labor. Other risks for the mother not increased in this study include preeclampsia, severe hypoglycemia, diabetic retinopathy, diabetic ketoacidosis, and progression of renal disease.^[21,22] Some patients had oligohydramnios and polyhydramnios.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study^[20] indicates strong, continuous associations

Table 7: Characteristics of the participants who had Type 1 diabetes mellitus

Characteristics/outcomes	HbA1c ≤6.5% (n=9)	HbA1c >6.5% (n=44)	P
Maternal characteristics, mean (SD)			
Age (years)	31.22 (7.55)	28.7 (6.34)	0.2978
Prepregnancy BMI	26.822 (3.832)	28.559 (5.567)	0.3774
Mean systolic BP ^a	117.89 (8.01)	121.43 (13.26)	0.4451
Mean diastolic BP ^a	74.33 (9.62)	75.93 (0.77)	0.6818
Mean blood glucose (mg/dl)	128.22 (9.39)	191.20 (31.43)	<0.0001
Mean HbA1c ^c (%)	6.0778 (0.3383)	8.27 (1.0839)	<0.0001
Duration of DM in years	14.889 (7.322)	11.420 (6.27)	0.1475
Family history of DM, number of patients (%)	2 (22.22)	15 (34.09)	0.7011
Multiparous ^b , number of patients (%)	4 (44.44)	16 (36.36)	0.7151
Obstetrical outcomes, number of patients (%)			
NSVD	5 (55.56)	7 (15.9)	0.0388
CS	4 (44.44)	30 (68.18)	
Miscarriages ^c	0 (0)	7 (19)	0.0491
Preterm labor <35 weeks (only singleton pregnancies)	0 (0)	11 (35.48)	0.0433
Polyhydramnios ^d	0 (0)	12 (27.27)	0.0995
Hypertension	0 (0)	4 (9.09)	1
Proteinuria	2 (22.22)	15 (34.09)	0.7011
Preeclampsia	0 (0)	1 (2.27)	1

^aMean HbA1c was defined as mean value of all the HbA1c readings got from each patient from baseline reading up to last prenatal visit, ^bMean blood pressure was defined as mean readings of blood pressure collected from the patient from the first clinic visit up to time before delivery, ^cMultiparous means >2 deliveries, ^dPolyhydramnios was defined as when the volume of amniotic fluid exceeds the norm for the gestational age which is diagnosed by ultrasound, ^eMiscarriage includes missed miscarriage, inevitable miscarriage, complete or incomplete miscarriage and threatened miscarriage, ectopic and molar pregnancy. DM: Diabetes mellitus, HbA1c: Glycated hemoglobin, NSVD: Normal spontaneous vaginal delivery included normal vaginal and assisted vaginal, CS: Cesarean section, SD: Standard deviation

Table 8: Characteristics of the newborn born to Type 1 diabetes mellitus mothers

Characteristics/outcomes	HbA1c ≤6.5% (n=9)	HbA1c >6.5% (n=44)	P
Newborn characteristics, mean (SD) (n)			
Gestational age at delivery (weeks)	38.78 (1.48) (9)	36.84 (2.52) (37)	0.0327
Birth weight (kg)	3.14333 (0.6119) (9)	3.25887 (.6252) (31)	0.6268
Apgar scores at 10 min	9.22 (0.83) (9)	9.1 (0.98) (31)	0.7291
Newborn outcomes, number of patients (%)			
IUFD/stillbirth	0 (0)	6 (16.21)	0.3273
Premature delivery <37 weeks gestation	1 (11.11)	11 (29.72)	0.0889
Macrosomia	1 (11.11)	6 (19.35)	1
perineal tear	0 (0)	4 (12.9)	0.5573
NICU ^a admission	1 (11.11)	6 (19.35)	1
Hypoglycemia	1 (11.11)	18 (58)	0.0238
Hyperbilirubinemia	1 (11.11)	4 (12.9)	1
Congenital anomaly	0 (0)	2 (6.45)	1

^aNICU: Neonatal Intensive Care Unit was defined by admission to any type of unit for care more intensive than normal newborn care. SD: Standard deviation, IUFD: Intrauterine fetal death, HbA1c: Glycated hemoglobin

Table 9: Odds ratio and 95% confidence interval of interactions between factors on maternal and fetal outcomes

Factor	OR (95% CI)			
	CS	Miscarriage	NICU admission	Macrosomia
GDM	1.999 (1.021-3.927) ^a	4.155 (1.003-19.836) ^a	3.713 (1.023-14.632) ^a	7.156 (2.542-21.156) ^a
T1DM	5.357 (0.91-33.815) ^a	Infinity (0.251-infinity) ^z	1.548 (0.14-39.139) ^z	1.548 (0.14-39.139) ^z
T2DM	6.875 (2.1-23.309) ^a	Infinity (1.187-infinity) ^a	2.75 (0.495-19.928) ^z	1.545 (0.332-8.056) ^z
Overall	3.486 (2.074-5.874) ^a	8.151 (2.322-34.148) ^a	3.488 (1.383-9.161) ^a	3.880 (1.764-8.738) ^a

^aNot significant ^zP<0.05. T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus, GDM: Gestational diabetes mellitus, OR: Odds ratio, CI: Confidence interval, CS: Cesarean section. Miscarriage includes missed miscarriage, inevitable miscarriage, complete or incomplete miscarriage, threatened miscarriage, ectopic, and molar pregnancy, NICU: Neonatal Intensive Care Unit was defined by admission to any type of unit for care more intensive than normal newborn care

of higher maternal glucose levels with increased birth weight above the 90th percentile for gestational age, increased primary CS, clinically diagnosed neonatal hypoglycemia, and cord-blood serum C-peptide level above the 90th percentile. Secondary outcomes were increased premature

delivery (before 37 weeks of gestation), shoulder dystocia or birth injury, NICU admission, hyperbilirubinemia, and preeclampsia. However, the HAPO study compared the GDM population against the normal population. Adverse pregnancy outcomes remain higher in DIP than in the

general population, especially if proper glucose levels are not maintained.^[20,23] This present study analyzed the diabetic population only and made comparison within each DM groups and on the basis of HbA1c values. A study done in Oman concluded that GDM patients had higher risk of CS and NICU admissions.^[24]

This retrospective study of DIP shows that irrespective of the type of DM, patients with HbA1c >6.5% had significantly shorter gestational period [Figure 2], with higher CS rates and significantly more miscarriages. Their neonates had significantly more macrosomia and hypoglycemia. GDM and Type 1 diabetic patients with HbA1c >6.5% had significantly more preterm deliveries. Risks are the same or higher in Type 2 diabetes compared to Type 1 diabetes.^[8,18,19]

The diabetes care and complications trial^[25] has demonstrated that stricter glycemic normalization reduces the frequency and severity of complications of T1DM and may improve pregnancy outcomes if women are in better glycemic control when they conceive. Therefore, all women with diabetes should be advised to plan their pregnancy and optimize glucose control. This agrees with this study as glucose control is maintained the rate of miscarriages go down significantly. There were no miscarriages in T1DM and T2DM patients and 3.19% of miscarriages in GDM patients with controlled HbA1c compared to 19%, 22.22%, and 12% in T1DM, T2DM, and GDM patients with higher HbA1c values, respectively. It is important to maintain near normal blood glucose level to reduce the odds of miscarriage and stillbirths which even though was not significant in some of the groups, however, increased when HbA1c levels were uncontrolled.

DIP is associated with preeclampsia,^[22] hydramnios, operative delivery, neonatal morbidities such as respiratory and metabolic complications and neonatal mortality.^[26] In

addition, there is increased risk of fetal macrosomia,^[27,28] congenital anomalies,^[29,30] birth traumas, and fetal organomegaly. Excellent blood glucose control during the period of conception and throughout pregnancy will reduce many of these risks.^[20,23]

This study did not show an increased risk of preeclampsia although proteinuria was more common in patients with HbA1c >6.5%. According to a study by Holmes *et al.*,^[22] increased HbA1c in T1DM patients is not significantly associated with gestational hypertension. This conforms with this present study which found that 9.43% ($n = 5$) patients were on antihypertensives with mean HbA1c 8.1 ± 1.45 in the T1DM group, in contrast with 15.78% ($n = 15$) patients on antihypertensives with mean HbA1c 7.6 ± 1.37 in the T2DM group. In this study, Group 1 had lower mean BP with only 7.14% on antihypertensive as opposed to 10.55% in Group 2. According to a study by Mello^[31] in DIP, only overall daily glucose values ≤ 95 mg/dl throughout the second and third trimesters can avoid alterations in fetal growth. We saw that as HbA1c values went up, the macrosomia rates went up, as did the likelihood of CS, especially in the GDM patients, there was a significant increase in macrosomia (35.21% vs. 7.058, $P < 0.0001$) while in the T1DM and T2DM groups, the results were not significant. The study showed adverse fetal outcomes such as higher NICU admission in the GDM group ($P = 0.0292$) and increased rate of miscarriages ($P = 0.040$) in concurrence with other studies.^[24,25] Likelihood of NICU admission was increased across all types of DM as HbA1c values went >6.5%.

In a systematic review^[32] of observational studies on HbA1c levels categorized into poor and optimal control with data addressing miscarriage, congenital malformations, and perinatal mortality among pregnant women with Type 1 and Type 2 diabetes, there was a relative risk reduction of anomalies for each 1% decrease in HbA1c. This study quantified the increase in adverse pregnancy outcomes in women with diabetes who have poor glycemic control.

Another systematic review^[33] and meta-analysis concluded that preconception care of T1DM and T2DM is effective in reducing diabetes-related congenital malformations, preterm delivery, and maternal hyperglycemia in the first trimester of pregnancy. This systematic review concluded that preconception care is effective in reducing congenital malformation, preterm delivery, and perinatal mortality and lowers HbA1c in the first trimester of pregnancy by an average of 2.43%. In this study, preconception care is very poor since the pregestational diabetes group had high mean HbA1c values compared to GDM group. Further, when the T1DM and T2DM patients had lower HbA1c

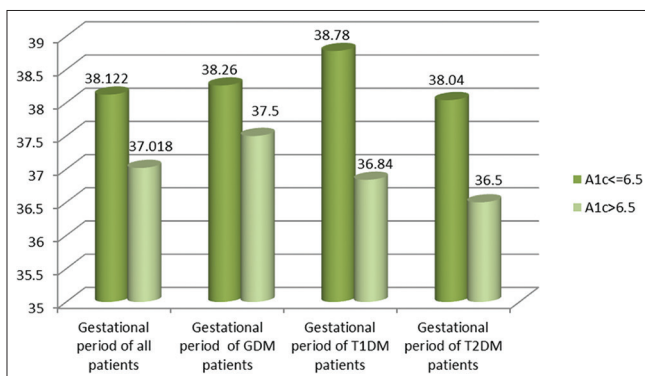


Figure 2: Differences in gestational period (in weeks) across different groups. HbA1c: Glycated hemoglobin, GDM: Gestational diabetes mellitus, T2DM: Type 2 diabetes mellitus, T1DM: Type 1 diabetes mellitus

values, there were no miscarriages. If normoglycemia was maintained before conception, then better pregnancy outcomes can be expected. This strengthens the need to have better preconception care in all known DM patients.

The ADA 2016 standards of care^[11] recommends a target of HbA1c 6–6.5% (42–48 mmol/mol) but states that 6% (42 mmol/mol) may be optimal as pregnancy progresses and HbA1c levels may need to be monitored more frequently than usual, i.e., monthly.

The strength of this study is that the population was a homogenous one. The limitation is that it covers only one center in Riyadh. The population does not coincide with the general makeup of GDM percentage because the study was done at a tertiary referral center.

CONCLUSIONS

In summary, poor glycemic control is associated with a greater risk of miscarriage, NICU admission, operative delivery, and shorter gestational periods. Especially at risk are those with preexisting diabetes, who would benefit from maintaining near normal glycemia before conception. All DIP patients would benefit by earlier referral to the diabetes service. Emphasis placed on the early detection and effective treatment of DIP to achieve normoglycemia if associated complications, perinatal mortality, and maternal morbidity are to be reduced. Earlier diagnosis, lifestyle management, and treatment of diabetes will reduce incidence and severity of hyperglycemia complications.

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Conflicts of interest

There are no conflicts of interest.

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