



Early-Onset of Gestational Diabetes vs. Late-Onset: Can We Revamp Pregnancy Outcomes?

**Nuzhat Parveen¹, Sehar-un-Nisa Hassan², Aqeela Zahra³, Naveed Iqbal¹, Asma Batool⁴*

1. Department of Obstetrics and Gynecology, College of Medicine, University of Ha'il, Ha'il-81451, Saudi Arabia
2. Department of Public Health, College of Public Health and Health Informatics, University of Ha'il, Ha'il-81451, Saudi Arabia
3. Department of Family and Community Medicine, College of Medicine, University of Ha'il, Ha'il-81451, Saudi Arabia
4. Maternity and Children Hospital Ha'il, Ha'il, Saudi Arabia

***Corresponding Author:** Email: n.parveen@uoh.edu.sa, drnparveen@yahoo.com

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Abstract

Background: We assessed risk factors, antenatal and intrapartum complications associated with early-onset Gestational diabetes mellitus (GDM) in comparison with late-onset GDM.

Methods: This retrospective study included 161 GDM women having singleton pregnancies, without previous medical disorder and delivered at a tertiary care Hospital in Ha'il City, KSA from Dec 2020 till Jun 2021. Women diagnosed at < 24 weeks of pregnancy were grouped as early-onset GDM (n=71) and those diagnosed at ≥ 24 weeks as late-onset GDM (n=90). Both groups were matched for background variables. Chi-square and binary logistic regression analysis were applied with *P*-value significance at 0.05.

Results: Past history of GDM, macrosomia and stillbirth were significant predictors for early-onset GDM (*P* value 0.000, 0.002 and 0.040 respectively). Regression analysis showed early-onset GDM significantly increases the risk for recurrent urinary tract infections (AOR 2.35), polyhydramnios (AOR 2.81), reduced fetal movements (AOR 2.13), intrauterine fetal demise (AOR 8.06), macrosomia (AOR 2.16), fetal birth trauma (2.58), low APGAR score at birth (AOR 8.06), and neonatal ICU admissions (AOR 2.65). Rate of preterm birth, hypertensive disorders, labor onset (natural vs. induced) and cesarean section and intrapartum maternal complications were same in both groups.

Conclusion: Early-onset GDM significantly increases certain maternal (recurrent urinary tract infections, polyhydramnios and reduced fetal movements) and fetal complications (intrauterine fetal demise, macrosomia fetal birth trauma, low APGAR score at birth and neonatal ICU admissions). Most of these adverse pregnancy outcomes can be prevented through early registration and screening, close follow up, growth ultrasounds, and provision of efficient emergency and neonatal care services.

Keywords: Gestational diabetes; Maternal outcome; Fetal outcome



Introduction

Gestational diabetes mellitus (GDM), an emerging public health concern especially in terms of pregnancy outcomes is defined as any degree of glucose intolerance first time recognized during pregnancy (1). Although reliable data is not available about the overall burden of GDM due to the lack of a uniform diagnostic criterion, few studies suggest that the global prevalence of GDM varies from 4.4% to 10.6% (2, 3). Saudi Arabia has an alarming prevalence of GDM that may link with the rapid shift in lifestyle and food habits in the past few decades. Analysis from Riyadh Mother and Baby Cohort Study suggests a prevalence rate of 24.2% for gestational diabetes (4). The incidence of GDM is continuously increasing due to an increase in the rate of obesity and type 2 diabetes, both of which are strong risk factors for GDM. Advanced maternal age, family history of diabetes, multiparity, and overweight babies in previous pregnancies are also reported as risk factors for GDM (5).

GDM is one of the common causes of pregnancy complications. It has numerous adverse fetomaternal effects during pregnancy, childbirth, and puerperium. Accelerated fetal growth (fetal macrosomia) associated with GDM leads to many adverse fetal effects as well as birth-related maternal complications (6). There is an increased risk of birth asphyxia, hypoglycemia, and need of Neonatal Intensive Care Unit (NICU) admissions in newborns of GDM mothers. Infants who are born to GDM mothers also at higher risk of obesity and type 2 diabetes at an earlier age (7). Maternal complications mostly include increased risk of pregnancy-induced hypertension (PIH)/ preeclampsia, polyhydramnios, preterm labor, delivery by cesarean section, postpartum hemorrhage, and progression to type 2 diabetes in long term (8, 9).

Paralleled to the growing burden of this disease, the controversies in its detection and management are increasing alongside. There are different diagnostic criteria (International Association of Diabetes and Pregnancy study Groups criteria,

standard WHO criteria) and management guidelines given by implementing bodies such as the American Diabetic Association and the WHO. Consequently, its screening, diagnosis, and management have become challenging.

Previous research studies in Saudi Arabia mostly focused on determining the prevalence of GDM in different cities and regions (10-12). Some studies analyzed the common risk factors which can cause GDM (13, 14). One study assessed the knowledge of women regarding GDM and its diagnosis (15). Few studies in Saudi Arabia identified the specific effects of GDM on the mother and fetus (16, 17). However, there is a gap in existing research to demonstrate differences regarding antenatal and intrapartum complications by comparing women with early and late-onset of GDM. Routine screening and diagnosis of GDM are recommended at 24 to 28 weeks of pregnancy. However, women with high fasting blood glucose levels and glycosuria at booking can be subjected to early diagnosis based on their risk identification (18,19). Pregnancy outcomes may vary according to the timing of the onset of GDM during pregnancy. It is important to determine these differences for improving pregnancy outcomes with early and late-onset GDM. Early diagnosis and early management can prevent and decrease many developmental problems during pregnancy.

We aimed to assess the rates of early and late-onset GDM in Ha'il City of Saudi Arabia. The current study will fill some of the gaps in research data in terms of fetomaternal outcomes of GDM with special emphasis on its time of onset.

Materials and Methods

We conducted this retrospective study at a tertiary care referral Hospital at Ha'il, Kingdom of Saudi Arabia (KSA), starting from Dec 2020 till Jun 2021. Pregnant women who registered early in pregnancy, were diagnosed as GDM during the antenatal period, and delivered at the facility were

included in the study. Women pregnant with multiple fetuses, with pre-existing diabetes, with other medical or obstetrical conditions, non-Saudis and cases with missing information in medical records were excluded.

The sample size comprised 166 GDM patients, Women who delivered twins (n=5) were excluded. A total of 161 women were enrolled in the study.

The information on prenatal risk factors and antenatal complications in the mother and fetus were recorded. Labor onset was considered natural, if labor started spontaneously without any intervention and induced, where pregnancy was terminated medically or surgically because of worsening pregnancy complications. Mode of delivery included spontaneous vaginal delivery (SVD) and cesarean-section (C-section). Intrapartum complications were also recorded. Fetal Macrosomia was defined as newborns with a birth weight of 4 kilograms or more. Responses for all these variables were recorded in the category of 'Yes' or 'No'.

Diagnostic criteria for GDM and Cutoff value for HbA1c: All participants were diagnosed using the WHO standard oral glucose tolerance test (OGTT) with a 75-gram glucose load, as per hospital policy. Plasma glucose levels were measured at fasting and 2-h after the load. Fasting plasma glucose 5.1-6.9 mmol/L (92 -125 mg/dl) and 2-h after the load 8.5-11.0 mmol/l (153 -199 mg/dl) level considered for diagnosis of GDM (18). For HbA1c, we used values recommended by National Institute for Health and Care Excellence (NICE) guidelines (19) and a cut-off of 6.1 used. HbA1c value 6.1 or less was considered as normal (well-controlled GDM), while above 6.1 was considered as high (uncontrolled GDM) during pregnancy (taken as a categorical variable).

Definition of Early and Late-onset GDM: Participants were divided into two groups based on the gestational age (in weeks) at which they were diagnosed with GDM. Women who were diagnosed before 24 weeks of pregnancy (subjected to early assessment for their risk factors and abnormal fasting blood glucose level or glycosuria at booking visit) based on NICE recom-

mendations (19) were categorized under "Early-onset GDM group" while those diagnosed at or after 24 weeks, were grouped as "Late-onset GDM".

The pre-pregnancy BMI was calculated for the women by measuring their height in centimeters and pre-pregnancy weight in kilograms. The BMI was calculated by using the formula, Weight in Kg/Height in (m)² and was analyzed as a categorical variable (Non-Obese: BMI <30 kg/m², Obese: BMI ≥ 30 kg/m²) (20).

Statistical Analysis

We used SPSS version 23; SPSS Inc., (IBM Corp., Armonk, NY, USA) for data analysis. Descriptive analysis was done to report the mean score, frequency, and percentage values for study variables. To compare the participants in Early-onset GDM and Late-onset GDM concerning background variables, mean differences were computed by using the Independent-Sample *t*-test. Chi-square test was applied to assess the relationship of early and late-onset GDM with prenatal risk factors, antenatal and intrapartum complications. Binary logistic regression analysis (95% confidence interval) was performed to determine the predictive nature of Early-onset GDM for antenatal and intrapartum complications during pregnancy. *P*-value <0.05 was taken statistically significant.

Ethics approval

The protocols of the study were reviewed and approved by the Research Ethics Committee of the University of Ha'il, KSA on 27th November 2020 by the university president's letter number (Nr.20455/5/42). The study was conducted according to the guidelines of the Declaration of Helsinki. Informed consent was obtained from the patients (when present in the hospital for delivery) after explaining the study's purposes and ensured that neither any content of their personal identification nor any source which can reach their identity (like medical record number) is required for this work.

Results

The study sample (n=161) included women of reproductive age (22 to 45 yr old) with a mean age of 35.4±5.4 yr. They were first to 10th gravi-

da with mean gravidity of 4.8±2.7 pregnancies, while mean parity was 0-9 children (2.94±2.2). The two comparison groups were matched for the mean age, parity, glycemic indices, and weight gain during pregnancy (Table 1).

Table 1: Comparison based on clinical characteristics of women with early and late-onset GDM(n=161)

<i>Variables</i>	<i>Early-onset GDM Mean± S.D.</i>	<i>Late-onset GDM Mean± S.D.</i>	<i>P value*</i>
Gestational age at diagnosis (weeks)	18.58± 5.2	31.5± 3.8	0.019
Age of the participants(years)	35.55±5.1	35.26±5.7	0.137
Parity	3.04± 2.1	2.86±2.2	0.725
Fasting BGL(mmol/L)	6.45± 1.1	6.35± 1.31	0.745
2-hours PP (mmol/L)	10.4± 1.6	9.82± 1.98	0.323
HBA1c	6.67± 1.77	6.24± 1.74	0.481
Weight gain during pregnancy (kg)	13.42± 5.7	13.46± 11.7	0.425

*P-value calculated by one way INOVA

The bivariate analysis (Table 2) shows the women who had GDM in previous pregnancies are at significantly increased risk of developing Early-onset GDM in subsequent pregnancy as well. While higher proportions of women without previous GDM (60%) had late-onset. Similarly, past history of babies ≥4kg(macrosomia) was also found significant for the early development of GDM. Past history of Cong. abnormalities was

also significant for prediction of Early-onset GDM. The previous history of stillbirth had a significant association for early-onset GDM. Other variables (presence of DM in first-degree relatives, obesity, and previous evidence of intra-uterine death in late pregnancy) demonstrate the non-significant difference between the two groups.

Table 2: Bivariate analysis showing relationship of prenatal risk factors with the early-onset of GDM

<i>Prenatal Risk factors</i>	<i>Early-onset GDM (n=71) N(%)</i>	<i>Late-onset GDM (n= 90) N(%)</i>	<i>P value</i>
History of GDM	49(69)	36(40)	0.000
Good size babies≥4kg	40(56.3)	29(32.2)	0.002
Cong. abnormalities	8(11.2)	2(2.2)	0.021 ¹
Still births	14(19.7)	8(8.8)	0.040
Late IUFD	16(22.5)	12(13.3)	0.094
DM in first degree relatives	64(90.1)	83(92.2)	0.424
Pre pregnancy Obesity	51(71.8)	56(62.2)	0.132

¹1 cell 25 % have expected count less than 5

The association of early and late-onset of GDM with complications during the antenatal period is

shown in Table 3. Early-onset of GDM had significant association with recurrent UTIs.

Table 3: Antenatal complications with relation to onset of GDM

<i>Antenatal complications</i>	<i>Early-onset GDM(n=71) n(%)</i>	<i>Late-onset GDM(n=90) n(%)</i>	<i>P value</i>
Recurrent UTIs	57(80.2)	57 (63.3)	0.014
Pregnancy induced hypertension	9 (12.6)	13(14.1)	0.466
Pre-eclampsia	9(12.6)	12 (13.3)	0.547
Pre-term Labor	13(18.3)	13(14.4)	0.326
Growth restriction	4(5.6)	8(8.8)	0.320
Polyhydramnios	20(28.1)	11(12.2)	0.010
Reduced Fetal Movement	32 (45)	25 (27.7)	0.017
Intrauterine fetal demise	11(15.4)	2(2.2)	0.002

In Table 4, a higher proportion of women with early-onset of GDM gave birth to babies (weigh-

ing 4 kg or more) as compared to late-onset (26.8% vs. 14.4%).

Table 4: Bivariate association of Early and Late-onset GDM with delivery events and intrapartum complications

<i>Delivery</i>	<i>Early-onset GDM(n=71) n(%)</i>	<i>Late-onset GDM(n=90) n(%)</i>	<i>P value</i>
	Preterm birth		0.545
Preterm < 37 weeks	13(18)	16(18)	
Term ≥ 37 weeks	58(82)	74(82)	
	Labor onset		0.399
Natural onset	16(22.5)	23(25.6)	
Termination on medical or obstetrical indications	55(77.5)	67(74.4)	
	Mode of delivery		0.318
SVD	18 (25.4)	27(30)	
Cesarean section	53 (74.6)	63(70)	
	Neonatal weight		0.041
≥4 kg	19(26.8)	13 (14.4)	
<4kg	52 (73.2)	77 (85.6)	
Shoulder dystocia	5(7)	11 (12.2)	0.206
Extended/3 rd -degree tear	1(1.4)	3(3.3)	0.404 ¹
Immediate PPH	8(11.3)	8(9)	0.404
Fetal Birth trauma	2(2.8)	1(1.1)	0.411 ¹
Low fetal APGAR score at birth	11(15.5)	2(2.2)	0.002
NICU Admission	13(18.3)	7(7.8)	0.039

¹1 cell 25 % have expected count less than 5

Thus macrosomia was significantly associated with Early-onset GDM (P=0.041). More fetuses had low APGAR scores at the time of birth in the early-onset GDM group when compared to the late-onset group (15.5% vs. 2.2%; P=0.002). Similarly, more neonates of Early-onset GDM group mothers were admitted to ICU (18.3% vs. 7.8%) and the difference between the two groups was statistically significant (P <0.05).

Women with Early-onset GDM were 2.3 and 2.8 times at increased risk of recurrent UTIs and pol-

hydramnios respectively (Table 5). Furthermore, these women were 2.1 times more prone to have reduced fetal movements and 8 times at increased risk to intrauterine fetal deaths with a significant P-value. Among intrapartum fetal complications, low APGAR scores at birth and NICU admissions were more likely to occur in patients with early-onset GDM (AOR 8.06 and 2.6 respectively).

Table 5: Adjusted Odd Ratios to show the impact of Early-onset GDM on antenatal and intrapartum complications

Statistical Values	<i>Antenatal Complications</i>			
	Recurrent UTIs	PIH	Pre-Eclampsia	Pre-term Labor
AOR	2.35	0.86	0.94	1.32
95% CI	(1.142---4.86)	(0.345—2.143)	(0.374—2.383)	(0.573—3.078)
P	0.020*	0.746	0.902	0.509
Statistical Values	Growth Restriction	Polyhydramnios	Reduce Fetal Movement	IUFD
	AOR	0.61	2.81	2.13
95% CI	(0.177—2.12)	(1.2—6.367)	(1.106—4.114)	(1.726—37.701)
P	0.439	0.013*	0.024*	0.008*
Statistical Values	<i>Intrapartum Complications</i>			
	Shoulder Dystocia	Extended Perineal Tears	Immediate PPH	Macrosomia
AOR	0.54	0.41	1.30	2.16
95% CI	(0.18 – 1.64)	(0.24-4.07)	(0.46-3.6)5	(0.98-4.76)
P	0.281	0.450	0.617	0.055
Statistical Values	Fetal Birth Trauma	Low APGAR Score	NICU Admissions	
	AOR	2.58	8.06	2.65
95% CI	(0.22-29.03)	(1.72-37.7)	(0.99-7.06)	
P	0.43	0.008	0.050	

Discussion

Adverse pregnancy outcomes associated with GDM are well-known. However, inconsistent results have been published regarding its complications concerning its onset (21-22). Our study findings demonstrate that prenatal risk factors like history of GDM, macrosomia, stillbirths, and congenital malformations were associated with

early-onset GDM in the subsequent pregnancy. It signifies the need to screen women in early pregnancy based on their previous risk factors. Among the 161 participants, 44% had early-onset GDM. The prevalence of early-onset GDM is different in different studies (23). These variabilities are due to different settings, study populations, and diagnostic criteria.

While looking into the association of risk factors for early-onset of GDM women, nearly half had GDM in previous pregnancies as well. A recently conducted review study (24) also had a comparable GDM recurrence risk. It demands screening of all women with a positive history of GDM. Of these women, more than half developed it before 24 weeks of pregnancy and showed a significant association of recurrence with early-onset. Our study findings were inconsistent with a large study, where previous GDM was an equal risk for early and late GDM (25). Similarly, in another study, conducted on Iranian pregnant ladies, the history of GDM in previous pregnancy was the same in both (early and late) groups (26). The history of macrosomia (fetal weight ≥ 4 kg) was also significant for early-onset. A systematic review and meta-analysis performed from Asian studies also highlighted it as a significant risk factor to predict GDM in subsequent pregnancies (27). The finding demands that women with a history of macrosomia need to be subjected to early screening and diagnosis to achieve glycemic control during the early development phase of the conceptus. Addressing it before conception can aid in the detection and repair of glucose impairments even before the onset of pregnancy, preventing hyperglycemia during the early stages of pregnancy. Risk analysis from history showed that patients with previous congenitally abnormal babies and stillbirth are more likely to develop GDM early in the pregnancy. The Meta-analysis of studies conducted among Asian women published the same finding (27). It reflects the need for special attention to the patients with previous GDM, macrosomia, and congenital abnormalities or stillbirths, so that early intervention can improve the pregnancy outcomes.

Our analysis of antenatal complications against the onset of GDM showed that early-onset GDM was significantly associated with recurrent UTIs. Many studies conducted before show an association of diabetes during pregnancy and UTI, but an increased rate was seen in the pre-gestational DM group (28) compared with GDM. It reflected the high background risk of UTI during pregnancy superimposed by early-onset hy-

perglycemia and indicated the importance of early detection and timely interventions to reduce its occurrence during the antenatal period. Similarly, polyhydramnios was associated with diabetes during pregnancy in general and GDM in specific (29). When comparing the risk between early and late-onset GDM groups, the early-onset GDM had a significant association with polyhydramnios. Polyhydramnios has multifactorial etiology. Many fetal and maternal conditions including glycemic impairments can lead to amniotic fluid abnormalities during pregnancy. However, comparison studies conducted before showed variations. In one study it had no significant association with the timing of onset of GDM (23), while in another, polyhydramnios was more likely in late-onset GDM (30). Hence, further studies with control of confounding variables are necessary to reach a consistent statement. Reduced fetal movements are often preceded by intrauterine fetal death. We found a significant association of early-onset GDM for both reduced fetal movements and intrauterine fetal demise, reflecting the need for early and tight control of hyperglycemia to avoid these adverse fetal conditions. However, it was reported to be the same for the early and late-onset groups in a study (23) conducted in a neighboring country.

The prolonged exposure of the fetus to hyperglycemia, when left untreated, leads to fat deposition in the fetal body, resulting in macrosomia. It not only adds to intrapartum complications but also causes obesity among children in later life as well (7). Our study also showed a significant association of macrosomia with early-onset GDM similar to another study (31). Macrosomia in turn can cause many birth-related complications for mothers and fetuses as well. Neonatal birth trauma is one of those and we observed its significant association with Early-onset GDM. Thus control of macrosomia can be rewarding in terms of preventing these complications. Contrast results had been published in the past (23) where macrosomia was more common in late-onset GDM group. The reason behind this might be early interventions for blood sugar control and increased physical activity in that particular group.

Gestational diabetes mellitus had been related to a higher risk of intrapartum complications (32). Regarding intrapartum fetal complications, early GDM has been associated with increased risk (AOR 8.06) of low APGAR score at birth and 2.65 times increased risk of NICU admissions of the baby, in line with the previous literature (33). Findings suggest the need to give special attention to women with early-onset GDM at the time of delivery. Availability of a neonatal resuscitation team at the time of birth can prevent adverse outcomes in terms of early neonatal morbidity and mortality. In addition, NICU admission can be reduced by good glycemic control in early-onset GDM women during the course of their pregnancy. It will not only improve fetal and maternal health but also reduce the burden on healthcare resources.

Conclusion

Hearth care interventions should be directed to prevent early-onset GDM by addressing the risk factors during preconception and early pregnancy. There's a great need to target management strategies to achieve better and tight control of blood glucose levels if GDM arises early in the pregnancy. Many complications identified in the early-onset GDM are developmental (macrosomia, polyhydramnios, issues of fetal wellbeing in utero and at the time of birth) which takes time to reach a point of intricacy. The targeted and aggressive approach to identifying at-risk women, identifying these problems earlier, and providing timely treatment may prevent their occurrence and their negative consequences as well. This can be achieved by early registration, early screening and diagnosis, frequent checkups, growth ultrasounds, and the provision of efficient emergency care services to these high-risk pregnant women.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or fal-

sification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors

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Conflict of interest

The authors declare that there is no conflict of interest.

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