

# The effect of different forms of dysglycemia during pregnancy on maternal and fetal outcomes in treated women and comparison with large cohort studies

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**Summary.** *Aims of the study:* We describe the impact of different forms of dysglycemia on maternal and neonatal health. This research is a part of the PEARL-Peristat Maternal and newborn registry, funded by Qatar National Research Fund (QNRF) Doha, Qatar. *Methods:* A population-based retrospective data analysis of 12,255 women with singleton pregnancies screened during the year 2016-2017, of which 3,027 women were identified with gestation diabetes mellitus (GDM) during pregnancy and 233 were diabetic before pregnancy. Data on maternal outcome was collected from the PEARL-Peristat Maternal and newborn registry. *Results:* The prevalence of GDM and diabetes mellitus (DM) was 24.7 % and 1.9%, respectively. 55% of DM, 38% of GDM and 25.6% of controls were obese ( $p < 0.001$ ). 71% of pregnant women with DM and 57.8% of those with GDM were older than 30 years versus 44.2% of controls. Pregnant women with DM or GDM had higher prevalence of hypertension versus normal controls (9.9%, 5.5% and 3.5%, respectively;  $p < 0.001$ ). Among women with vaginal deliveries, the proportion of women with induction of labor was significantly higher in the DM and GDM compared to control subjects (33.9%, 26.5% and 12.4%, respectively;  $p < 0.001$ ). The number of women who underwent Cesarean section was significantly higher in the DM and GDM groups versus normal controls (51.9%, 36.8%, and 28.5%, respectively;  $p < 0.001$ ). Preterm delivery was significantly higher in women with DM and GDM (13.7% and 9%, respectively versus normal women (6.4%);  $p < 0.001$ ). Babies of DM and GDM had significantly higher occurrence of respiratory distress (RDS) or transient tachypnea (TTS): 9% and 5.8 % versus normal controls (4.8%). Macrosomia was more prevalent in babies of DM (6.4%) and GDM (6.8%) compared to controls (5%) ( $p < 0.001$ ). Significant hypoglycemic episodes occurred more frequently in babies of DM and GDM women (11.2% and 3%, respectively) versus controls (0.6%) ( $p < 0.001$ ). Infants of DM and GDM mothers required more treatments of phototherapy (9.4% and 8.9%, respectively) versus those born to normal women (7.2%) ( $p = 0.006$ ). The prevalence of congenital anomalies and neonatal death did not differ between the groups. *Conclusions:* Despite the improvement in the prenatal diagnosis and management of dysglycemia, there is still a higher prevalence of prematurity, macrosomia, and hypoglycemia in infants of mothers with DM and GDM. Measurements to reduce obesity and control dysglycemia in women during the childbearing period are highly required to prevent the still higher morbidity during pregnancy. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** diabetes mellitus, dysglycemia, fetal, maternal, pregnancy, outcomes

## Introduction

In 1999, WHO stated that gestation diabetes mellitus (GDM) encompass from impaired glucose tolerance to diabetes (fasting  $\geq 7$  mmol/l or  $\geq 126$  mg/dl; 2 h plasma glucose  $\geq 7.8$  mmol/l or 140 mg/dl) and this position has been maintained over the years (1).

More recently, the International Association of the Diabetes in Pregnancy Study Group (IADPSG), after extensive analyses of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, recommended new diagnostic criteria for GDM based on the 2 h, 75 g OGTT: a fasting glucose  $\geq 5.1$  mmol/L (92 mg/dl), or a one hour result of  $\geq 10.0$  mmol/L (180 mg/dL), or a two hour result of  $\geq 8.5$  mmol/L (153 mg/dL) (2, 3).

The purpose of this study is to report the association of diabetes mellitus (DM) and GDM, as diagnosed by the IADPSG criteria, with different pregnancy outcomes, in treated women with GDM and in women with pre-existing DM in Qatar. In addition, our results are compared with other large cohort studies published in different countries.

## Patient and Methods

Data were derived from Qatar Perinatal Registry, developed in 2011, and reactivated in 2016 as Qatar PEARL-Peristat Registry. It was funded by Qatar National Research Fund (QNRF) and sponsored by the Medical Research Center (MRC) of Hamad Medical Corporation, Doha (Qatar). The registry contains abstracted data of routinely collected hospital data from all hospitals with delivery facilities in Qatar, spanning the perinatal to postpartum periods. By utilizing patient care records, the registry aims to examine the short and long-term maternal and newborn health outcomes. In addition, the study aims to explore the development of specified sub-cohorts with intent of improving reproductive health outcomes of the Qatar population. The registry houses delivery cohorts from 2011 to 2012, as the first phase, and currently 2017 to 2019, as a second phase, with the current phase targeting around 35,000 deliveries within the whole country. Data collection for the current phase is still ongoing.

For the current study, data for women with singleton births and completed record abstraction, between January - August 2017, were analyzed. 12,255 singleton pregnant women were identified of which, 3,027 women were identified with GDM and 233 with DM before pregnancy, according to the criteria of the International Association of the Diabetes in Pregnancy Study Group (IADPSG) (4).

## Management of diabetes during pregnancy

All pregnant women with dysglycemia were managed by multi-disciplinary care teams, including 2-3 examinations by diabetologists during pregnancy. Women enrolled in outpatient GDM management received one-on-one education/counseling and individualized GDM plan of care designed by certified diabetes educators (CDE). Education and counseling provided by the CDE included information on blood glucose testing, diabetes diet, exercise, and self-care activities. Every patient had a glucometer at home and was advised to do self-monitoring of blood glucose. Patients with multi-doses injections of insulin were advised to monitor the glucose levels 6-7 times per day (fasting blood glucose, pre-meals, 2 hours after meals and before bedtime). Patients on metformin or single dose of basal insulin were advised to monitor the glucose levels 4 times per day (fasting before meals, and before bedtime). The target blood sugar levels were as follows: a fasting blood glucose  $\leq 5.3$  mmol/l ( $\leq 95$  mg/dL) and 2 hours after meals  $\leq 6.7$  mmol/l ( $\leq 120$  mg/dL) without hypoglycemia. Patients on insulin treatment were advised to keep their capillary blood glucose above 4 mmol/l (72 mg/dL) and to monitor hemoglobin A1c (HbA1c). Hb A1c was measured in the first clinic visit and at least once in each trimester with a target HbA1c =  $\leq 6.5\%$ .

## Variables

The following maternal data were included: maternal age at delivery, parity, nationality, body mass index (BMI), duration of gestation, mode of delivery, induction of labor, hypertensive disorders in pregnancy

and any adverse effects on the mother. Neonatal data included: birth weight, gestational age, birth status (live born/stillborn), gender, preterm, macrosomia, admission to neonatal intensive care unit, blood glucose status, bilirubin status, phototherapy treatment, respiratory status, neonatal death and congenital anomalies.

Hypertension that was present before 20 weeks gestation and did not progress to preeclampsia was classified as chronic hypertension. Hypertensive disorders occurring after 20 weeks were categorized according to the International Society for the Study of Hypertension guidelines. Preeclampsia was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mm Hg on two or more occasions at least 6 h apart and proteinuria  $\geq 1+$  on dipstick or  $\geq 300$  mg to 24-h urine collection. If the criteria for elevated blood pressure were met without proteinuria, this was classified as gestational hypertension (5).

Preterm delivery was defined as delivery prior to 37 weeks gestation. Macrosomia was defined as birth weight  $\geq 4$  kilogram. Clinical neonatal hypoglycemia was defined by one or more clinical criteria: the presence of neonatal hypoglycemia registered in the medical record and symptoms or treatment with a glucose infusion or a laboratory-reported glucose value  $\leq 1.7$  mmol/L in the first 24 h after birth or  $\leq 2.5$  mmol/L after the first 24 h (6).

## Results

The prevalence of GDM and DM was 24.7% and 1.9%, respectively (Table 1). Seventy-one percent of pregnant women with DM and 57.8% of those with GDM were older than 30 years versus 44.2% of those with normal glycemia (Figure 1A). Fifty-five percent of DM, 38% of GDM and 25.6% of controls were obese ( $p < 0.001$ ) (Figure 1B). Pregnant women with DM and GDM had higher prevalence of hypertension versus normal controls (9.9%, 5.5% and 3.5%, respectively;  $p < 0.001$ ). Among women with vaginal deliveries, the proportion of women who underwent induction of labor was significantly higher in DM and GDM subjects compared to controls (33.9%, 26.5% and 12.4%, respectively;  $p < 0.001$ ). The number of women who underwent Cesarean section was sig-

nificantly higher in the DM and GDM groups versus normal controls (51.9%, 36.8%, and 28.5%, respectively;  $p < 0.001$ ) (Table 1 and Figure 1C).

Babies of DM and GDM women required more frequent admission to Neonatal Intensive Care unit (NICU) (25% and 16%, respectively) versus control babies (12%) ( $p < 0.001$ ). Preterm delivery was significantly higher in women with DM and GDM (13.7% and 9%, respectively) versus normal women (6.4%) ( $p < 0.001$ ) (Figure 1D). Macrosomia was more prevalent in babies of DM (6.4%) and GDM (6.8%) women compared to controls (5%) ( $p < 0.001$ ) (Table 2 and Figure 1D).

Significant hypoglycemic episodes occurred more frequently in babies of DM and GDM women (11.2%, and 3%, respectively) versus controls (0.6%) ( $p < 0.001$ ) (Figure 1F). Babies of DM and GDM mothers required more phototherapy (9.4% and 8.9%, respectively) versus those of non-diabetic women (7.2%) ( $p = 0.006$ ).

The prevalence of neonatal death and congenital anomalies did not differ significantly between the babies of DM and GDM mothers and babies of non-diabetic women (Table 2).

## Discussion

Gestational diabetes mellitus (GDM) is a heterogeneous disorder that is defined as carbohydrate intolerance with first recognition during pregnancy. GDM is a common medical problem that results from an increase in the insulin resistance as well as an impairment of the compensatory increase in insulin secretion from the  $\beta$ -cells of the pancreas. GDM is linked with a variety of maternal and fetal complications, most notably macrosomia, prematurity, neonatal hypoglycemia, respiratory distress, and more admission to NICU. Controlling maternal blood sugar with medical nutrition therapy, close monitoring of blood glucose levels and treatment with insulin to control blood glucose has been shown to decrease fetal and maternal morbidities.

GDM is a result of the interaction between genetic and environmental risk factors. Increased body fat and high caloric diet contribute to the risk of GDM; patients who lose weight before pregnancy and follow an appropriate diet may lower the GDM risks (7-9).

**Table 1.** Maternal and neonatal demographics

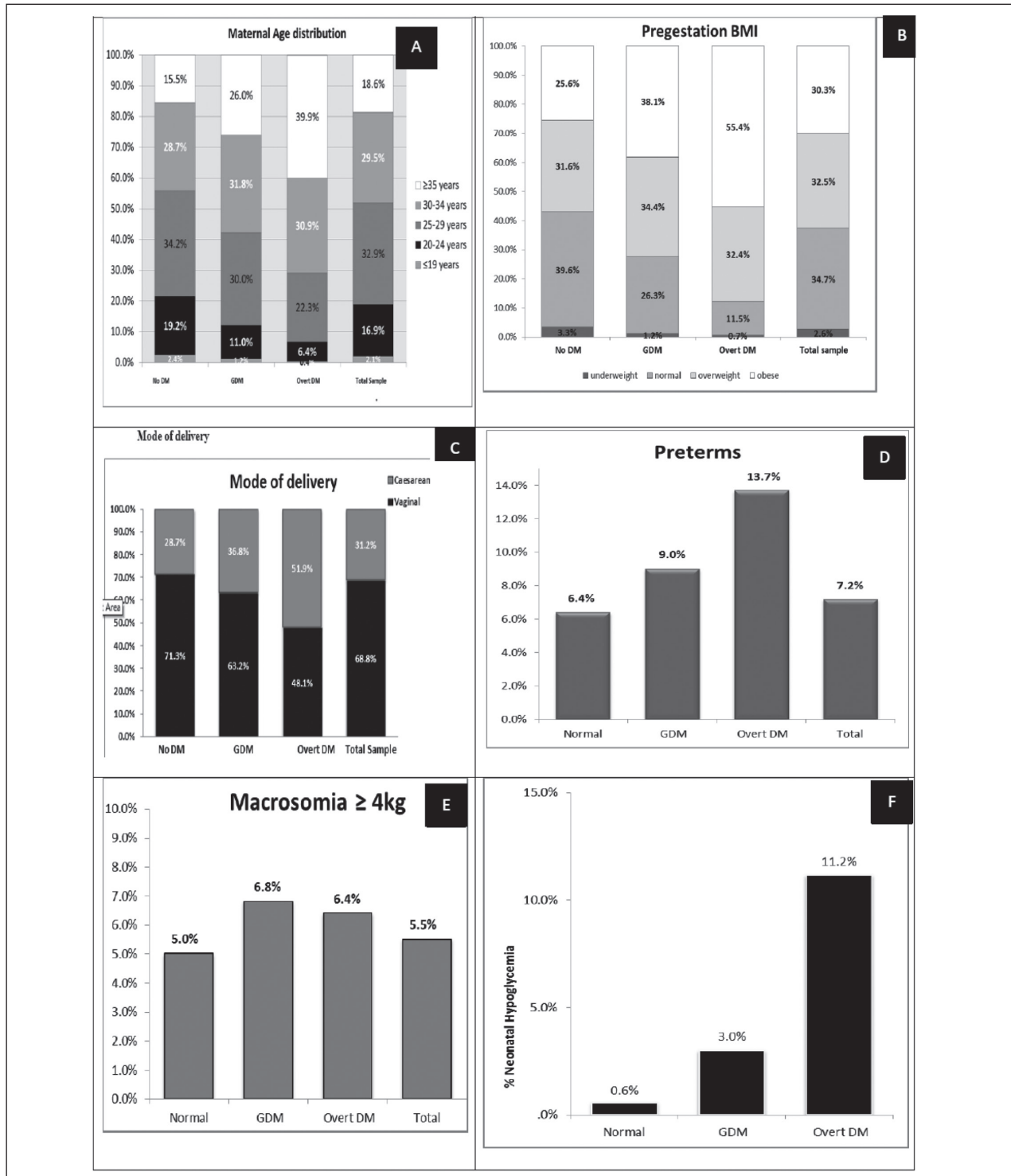
	DM comparison groups								$\chi^2$	P-value
	No DM (n=8995)		GDM (n=3027)		Overt DM (n=233)		Total (n= 12255)			
	n	%	n	%	n	%	n	%		
<b>Maternal age</b>										
≤19 years	220	2.4	35	1.2	1	.4	256	2.1	347.975	<.001
20-24 years	1728	19.2	332	11.0	15	6.4	2075	16.9		
25-29 years	3074	34.2	909	30.0	52	22.3	4035	32.9		
30-34 years	2578	28.7	964	31.8	72	30.9	3614	29.5		
≥35 years	1395	15.5	787	26.0	93	39.9	2275	18.6		
<b>Parity</b>										
Nulliparous	2702	30.0	737	24.4	46	19.7	3485	28.4	44.896	<.001
Parity ≥1	6290	70.0	2289	75.6	187	80.3	8766	71.6		
<b>Nationality</b>										
Qatari	2244	25.0	701	23.2	76	32.6	3021	24.7	11.994	.002
Non-Qatari	6749	75.0	2325	76.8	157	67.4	9231	75.3		
<b>Pre-gestation BMI*</b>										
Underweight	103	3.3	17	1.2	1	.7	121	2.6	175.307	<.001
Normal	1234	39.6	381	26.3	16	11.5	1631	34.7		
Overweight	985	31.6	498	34.4	45	32.4	1528	32.5		
Obese	797	25.6	552	38.1	77	55.4	1426	30.3		
<b>Hypertensive disorders</b>										
None	8683	96.5	2862	94.5	210	90.1	11755	95.9	43.097	<.001
Yes	312	3.5	165	5.5	23	9.9	500	4.1		
<b>Delivery</b>										
Vaginal	6409	71.3	1912	63.2	112	48.1	8433	68.8	116.965	<.001
Caesarean	2584	28.7	1115	36.8	121	51.9	3820	31.2		
<b>Induction of labour ‡</b>										
No	5612	87.6	1406	73.5	74	66.1	7092	84.1	244.308	<.001
Yes	797	12.4	506	26.5	38	33.9	1341	15.9		
<b>Birth Status</b>										
Liveborn	8926	99.2	3018	99.7	233	100.0	12177	99.4	7.754	.005†
Stillborn	69	.8	9	.3	0	0.0	78	.6		
<b>Newborn Gender</b>										
Male	4567	50.8	1547	51.1	128	54.9	6242	50.9	1.631	.442†
Female	4427	49.2	1478	48.8	105	45.1	6010	49.0		
Ambiguous	1	.0	2	.1	0	0.0	3	.0		
<b>Immediate Disposition</b>										
Postnatal ward	7825	87.8	2530	83.9	174	75.0	10529	86.6	58.302	<.001
NICU	1076	12.1	483	16.0	58	25.0	1617	13.3		
Died in LR/OT	12	.1	1	.0	0	0.0	13	.1		

\*Available for 38% of sample population

† Empty cell group or category excluded from chi-square analysis

‡Induction of labour within vaginal deliveries only

LR (labour room), OT (operating theatre)



**Figure 1.** A: Maternal age distribution in the different groups (DM, GDM, normal (No DM) and total; B: Pre-gestation BMI in the different groups (DM, GDM, normal (No DM) and total; C: Mode of delivery in in the different groups (DM, GDM, Normal (No DM) and total; D: Prevalence of premature labor in the different groups (DM, GDM, normal (No DM) and total; E: Prevalence of macrosomia in newborns of the different groups (DM, GDM, normal (No DM) and total; F: Prevalence of hypoglycemia in the newborns of the different groups (DM, GDM, normal (No DM).

**Table 2.** Neonatal outcomes within groups

	DM comparison groups (live births only)								$\chi^2$	P-value
	No DM (n=8926)		GDM (n=3018)		Overt DM (n=233)		Total (n= 12177)			
	n	%	n	%	n	%	n	%		
<b>Low Birth weight</b>										
≤2499 g	594	6.7	192	6.4	17	7.3	803	6.6	.505	.777
≥2500 g	8331	93.3	2826	93.6	216	92.7	11373	93.4		
<b>Macrosomia</b>										
<4000 g	8478	95.0	2813	93.2	218	93.6	11509	94.5	14.288	.001
≥4000 g	447	5.0	205	6.8	15	6.4	667	5.5		
<b>Preterm</b>										
Not preterm	8353	93.6	2747	91.0	201	86.3	11301	92.8	37.358	<.001
Preterm	573	6.4	271	9.0	32	13.7	876	7.2		
<b>Phototherapy</b>										
No	8280	92.8	2748	91.1	211	90.6	11239	92.3	10.276	.006
Yes	646	7.2	270	8.9	22	9.4	938	7.7		
<b>Hypoglycemia</b>										
No	8876	99.4	2928	97.0	207	88.8	12011	98.6	267.901	<.001
Yes**	50	.6	90	3.0	26	11.2	166	1.4		
<b>RDS/TTN</b>										
No	8495	95.2	2843	94.2	212	91.0	11550	94.9	11.606	.003
Yes**	431	4.8	175	5.8	21	9.0	627	5.1		
<b>Congenital Anomalies</b>										
No	8846	99.1	2986	98.9	230	98.7	12062	99.1	.948	.623
Yes**	80	.9	32	1.1	3	1.3	115	.9		
<b>Neonatal Death</b>										
No	8899	99.7	3013	99.8	233	100.0	12145	99.7	1.58	.209†
Yes	27	.3	5	.2	0	0.0	32	.3		

\*\*These babies were admitted to NICU

† Empty cell group excluded from chi-square analysis

RDS (respiratory distress syndrome), TTN (transient tachypnea of newborn)

The reported prevalence of GDM varies widely from 1% to 14% of all pregnancies. Our cohort consisted of 25% Qatari and 75 % non-Qatari women. Data showed a high prevalence of GDM compared to most of the published studies in different countries using the criteria of the International Association of the Diabetes in Pregnancy Study Group (IADPSG) for diagnosing GDM (Table 3) (10-21).

This can be explained in part by the high prevalence of obesity and overweight in our cohort com-

pared to others. Fifty-five percent of our patients who suffered from DM, 38% from GDM and 25.6% from controls were obese. A review and a meta-analysis by Torloni et al. (12) revealed that the relative risks for developing GDM (RR) measured for overweight, moderately obese and morbidly obese women (pre-pregnancy BMI) were 1.97 (95% CI 1.77 to 2.19), 3.01 (95% CI 2.34 to 3.87) and 5.55 (95% CI 4.27 to 7.21), respectively. For every 1 kg/m<sup>2</sup> increase in BMI, the prevalence of GDM increased by 0.92% (95% CI

**Table 3.** Main characteristics of previous published studies (Ref. 12-23) in comparison to our study

Study	Country	Number	Prevalence of GDM	Maternal Age (Yr.-mean± SD)	Pre-Gravid BMI
Alberg (2001)	Sweden	4,773	5.2%	NR	NR
Black (2010)	USA	8,711	19.4%	29.1±5.9	27.5±6.1
EBDG (2001)	Brazil	4,998	7.5%	27.8±5.5	23.4±4
Forsbach (1997)	Mexico	667	16%	18-44	NR
HAPO (2008,2010)	Multi-countries	23,316	11.4%	29.2±5.8	27.7±5.1
Khan (1994)	Pakistan	1,278	4.9%	26.7±4.6	NR
Shirazian (2008)	Iran	670	12.1%	NR	NR
Sugaya (2000)	Japan	416	32.5%	30.3±4.3	25.4±8.2
Soliman (2018)	Qatar	12,255	24.7%	29±5	27.5±5.8

NR = not reported

0.73 to 1.10). The risk of GDM was positively associated with pre-pregnancy BMI. In addition, it appeared that genetic background and other environmental factors were additional risk factors for developing GDM in Qatar.

A cross-sectional analysis of 3,017 Qatari subjects from the Qatar Biobank, identified 749 women, aged 18-40 years, 720 of whom were assessed. Prediabetes [HbA1c: 5.7-6.4 % and/or impaired fasting glucose (IFG: 100-125 mg/dL; 5.6-6.9 mmol/L), and T2DM (fasting plasma glucose >125 mg/dL; ≥7 mmol/L), and/or HbA1c ≥6.5%] were determined. The prevalence of prediabetes was 10.6%, and the prevalence of DM was found to be 4.0% of the total population. Obesity appeared to be an important risk factor for the development of DM. (BMI ≥30, adjusted OR = 2.2; 95% CI = 1.5-3.2; p<0.0001) (22, 23).

The relative incidence (RR) of preeclampsia, perinatal mortality, macrosomia, Caesarean section, among women with and without gestational diabetes were compared to large cohorts of subjects published in the literature (Table 4) (24-26). Neonatal Complications of GDM in our study were different compared to other studies with larger cohort (Table 5) (27-31). Macrosomia and/or large for gestational age (LGA) was the predominant adverse outcome associated with maternal hyperglycemia. In addition, macrosomia was the main reason underlying birth trauma and preterm birth, difficult labor and cesarean delivery. Treatment of GDM is supposed to decrease the risk of fetal macrosomia (32-36). Although macrosomia occurred more frequently in the babies of GDM versus control mothers, the prevalence of macrosomia in our cohort was lower than those reported by many other studies

**Table 4.** Relative incidence (RR) of pre-eclampsia, perinatal mortality, macrosomia, and Cesarean section, among women with and without gestational diabetes (Ref. 29-31)

	Pre-eclampsia/Hypertension		Perinatal mortality		C-section		Macrosomia	
	GDM	Non-GDM	GDM	Non-GDM	GDM	Non-GDM	GDM	Non-GDM
Forsbach, 1997				NR			10%	5%
Sugaya, 2000				NR			16.3%	12.8%
Alberg, 2001		NR	0.7%	0.2%	13.9%	7.9%	9.9%	4.5%
EBDG, 2001	3.13%	2.2%	0.36%	0.24%	47%	37.2%	17%	11%
HAPO, 2008		NR			24.4%	17.2%		
Shirazaian, 2008	NR						3.6%	3.3%
HAPO, 2010	7.6%	4.93%		NR				
Sugaya, 2010	27.3%	18.1%		NR				
Black, 2010	10.9%	7%		NR				
Soliman, 2018	5.5%	3.5%	0.4%	1.1%	36.8%	28.7%	6.8%	5%

NR = not reported

**Table 5.** Neonatal complications of GDM in different studies (Ref. 32-37)

	Assaf-Balut (2016)	González-Quintero (2007)	Amanda (2017)	Sreelakshmi (2015)	Garcia-Patterson (2012)	Prakash (2017)	Soliman (2018)
GDM number	542	3218	705	60	2,092	126	3,018
Prematurity	6%	ND	7.1%	10%	9.7%	11%	9%
Hypoglycemia	NR	7.2% in CGDM 9.3% in NCGDM	ND	NR	3%	4.5%	3%
Hyperbilirubinemia	NR	8.4 % in CGDM 10.1 % in NCGDM	ND	NR	NR	NR	8.9%
NICU admission	7.2	7.3% in CGDM 10.6% in NCGDM	5.1%	12%	NR	NR	16%
Still birth /Abortion		0.1% in CGDM 0.3% in NCGDM	0.4%	Stillborn 0.5% Abortion 19%	NR	4.5%	0.3%
Congenital anomalies	NR	NR	NR		NR	2.3%	1.1%

Abbreviations: CGDM = Controlled GDM, NCGDM= not controlled GDM, NR = not reported

(Table 4). This may be due to the proper use of the timed Caesarean section in our dysglycemic women, which relatively increased the prevalence of Caesarean section with no increase in the neonatal mortality compared to control mothers.

In the HAPO study (17), there were significantly greater odds of birth weight, newborn percent body fat and cord C-peptide >90th percentile, primary cesarean delivery, and preeclampsia for GDM or obesity alone compared with the reference group. The combination of GDM and obesity showed substantially higher ORs compared with those for either GDM or obesity alone. Shoulder dystocia or birth injury was uncommon (1.3% overall), and odds for these outcomes were significantly greater compared to reference group only when GDM and obesity were both present (29).

The risk for developing hypoglycemia among infants of diabetic mothers is higher than in non-diabetic mothers. Hypoglycemia occurs in approximately 8-30% of neonates of mothers with diabetes, with an estimated incidence rate of approximately 27% among infants of women with diabetes compared to 3% of healthy full-term infants of non-diabetic women. The full extent of the individual and contextual risk factors of hypoglycemia remains unclear. Both macrosomia and prematurity were suggested to contribute to the etiology of hypoglycemia in DM. The prevalence of hypoglycemia in babies of our GDM women was 3 %,

relatively lower compared to other studies. Our results also showed a prevalence of hypoglycemia (2.7 %) in macrosomia infants versus non-macrosomia infants (1.3%).

In our cohort, the prevalence of hypoglycemia was significantly higher in preterm infants (4.5%) compared to full-term infants (1.1%). In the HAPO study (17), there were no significant differences between the glucose determinations and A1c for the associations with clinical neonatal hypoglycemia. A1c showed a stronger association to FPG for preterm delivery (p: 0.003) but no difference compared with 1- or 2-h PG. Although the odds of clinical neonatal hypoglycemia rose through the first six categories of A1c, there was no independent association of A1c with birth weight >90th percentile or clinical neonatal hypoglycemia (30-31).

Comparing our neonatal outcome with those reported by Gonzalez et al. (32) on 3,218 women, we found that newborns of GDM women had a lower prevalence of hypoglycemia compared to the newborns of women with controlled GDM. This can be explained by our potent screening and management of pregnant women with GDM despite the proportionately high prevalence of GDM in our country (33-37).

Hypoglycemia occurred in approximately 8-30% of neonates of mothers with diabetes. The full extent of the individual and contextual risk factors of hypoglycemia remains unclear.



In a total of 16 eligible published research articles, the clinical risk was broadly classified into: infant-related and mother-related risk factors. The identified infant-related risk factors were: SGA, macrosomia, prematurity, lower cord blood glucose, ponderal index and male sex. On the other hand, mother-related risk factors included maternal hyperglycemia, ethnic origin, diabetes diagnosed prior to 28 weeks of gestation, pre-pregnancy BMI  $\geq 25$  kg/m<sup>2</sup>, blood glucose, maternal diabetes type and maternal HbA1c. Irrespective of diabetes type, infants of diabetic mothers appear to have a higher risk for developing hypoglycemia compared to control mothers (38).

Flores-le Roux et al. (39) prospectively examined the glucose levels in infants of women with GDM and the influence of maternal, gestational and peripartum factors on the development of hypoglycemia. They found that hypoglycemic infants were more frequently LGA (29.3% vs. 11.3%). Our data showed that hypoglycemia requiring NICU admission was more common in babies of DM (11.2%) and GDM (3%) compared to macrocosmic infants of control mothers (1.6%).

Garcia-Patterson et al. (40), using databases from a tertiary care center, examined the relationship between maternal pre-pregnancy BMI and hypoglycemia among infants of women with GDM and a gestational age above 22 weeks of gestation. The rate of neonatal hypoglycemia was 3%. Maternal pre-pregnancy BMI  $\geq 25$  kg/m<sup>2</sup> was determined as an independent predictor of hypoglycemia (41-43). Our study showed that 72.5% of mothers with GDM and 87.8% of mothers with DM had a BMI  $> 25$ .

A summary of the world literature (1930-1964) on malformations in infants of diabetic mothers showed that the number of malformation was 4.8% compared to 1.65% of controls (44).

In our study, congenital malformation occurred in 1.3% and 1.1% of newborns of diabetic mothers and GDM mothers, respectively, and was not different than those from the normal controls (0.9%). In support of these data, malformation rates in infants of gestational diabetic women have been published by many centers and there is general agreement that malformation rates are not increased. Furthermore, the Collaborative Perinatal Project (42) showed that the

malformation rates were 15.3% for whites and 13.7% for blacks. The corresponding rates for nondiabetics were 14.6 and 17.0%, respectively. The differences were not significant. This study clearly demonstrates that those without diabetes prior to pregnancy are not at increased risk for having malformed infants.

## In conclusion

Improvement in the diagnosis and management of pregnant women with dysglycemia lead to marked improvement in the neonatal outcome with a reduction in the rate of macrosomia, hypoglycemia, NICU admission and congenital malformations. However, there is still a higher prevalence of these comorbidities in infants of DM and GDM compared to normal women. Obesity and overweight in women during the childbearing period appears to contribute to the occurrence of high rates of dysglycemia during pregnancy. Measurements to reduce obesity during the childbearing period and control accurate glucose control during pregnancy are highly required to prevent any morbidity during pregnancy of women with DM and GDM.

## References

1. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539-53.
2. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, et al: Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; 358: 1991-2002.
3. Maryns AS, Dehaene I, Page G. Maternal and neonatal outcomes in a treated versus non-treated cohort of women with Gestational Diabetes Mellitus according to the HAPO 5 and 4 criteria. *Facts Views Vis Obgyn* 2017; 9: 133-40.
4. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva A, Hod M, Kitzmiller JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; 33: 676-82.
5. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the Interna

- tional Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; 20: IX–XIV.
6. Alkalay AL, Sarnat HB, Flores-Sarnat L, Elashoff JD, Farber SJ, Simmons CF. Population meta-analysis of low plasma glucose thresholds in full-term normal newborns. *Am J Perinatol* 2006; 23: 115–9.
  7. Imam K. Gestational diabetes mellitus. *Adv Exp Med Biol* 2012; 771: 24–34.
  8. Kramer CK, Swaminathan B, Hanley AJ, Connelly PW, Sermer M, Zinman B, Retnakaran R. Each degree of glucose intolerance in pregnancy predicts distinct trajectories of  $\beta$ -cell function, insulin sensitivity, and glycemia in the first 3 years postpartum. *Diabetes Care* 2014; 37: 3262–9.
  9. Shaat N, Groop L. Genetics of gestational diabetes mellitus. *Curr Med Chem* 2007; 14: 569–83.
  10. Torloni MR, Betrán AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, Valente O. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obes Rev* 2009; 10: 194–203.
  11. Aberg A, Rydhstroem H, Frid A. Impaired glucose tolerance associated with adverse pregnancy outcome: a population-based study in southern Sweden. *Am J Obstet Gynecol* 2001; 184: 77–83.
  12. Black MH, Sacks DA, Xiang AH, Lawrence JM. Clinical outcomes of pregnancies complicated by mild gestational diabetes mellitus differ by combinations of abnormal oral glucose tolerance test values. *Diabetes Care* 2010; 33: 2524–30.
  13. Forsbach G, Cantu-Díaz C, Vazquez-Lara J, Villanueva-Cuellar MA, Garcia C, Rodriguez-Ramirez E: Gestational diabetes mellitus and glucose intolerance in a Mexican population. *Int J Gynaecol Obstet* 1997; 9: 229–32.
  14. Schmidt MI, Duncan BB, Reichelt AJ, Branchtein L, Matos MC, Costa e Forti A, Spichler ER, Pousada JM, Teixeira MM, Yamashita T; Brazilian Gestational Diabetes Study Group. Gestational diabetes mellitus diagnosed with a 2-h 75-g oral glucose tolerance test and adverse pregnancy outcomes. *Diabetes Care* 2001; 4: 1151–5.
  15. Yogeve, Chen, Hod, Coustan, Oats, McIntyre, Metzger, Lowe, Dyer, Dooley, Trimble, McCance, Hadden, Persson, Rogers; Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: preeclampsia. *Am J Obstet Gynecol* 2010; 202: 255–7.
  16. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes* 2009; 58: 453–9.
  17. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR, Trimble ER, Coustan DR, Hadden DR, Hod M, Oats JJ, Persson B; HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations of maternal A1C and glucose with pregnancy outcomes. *Diabetes Care* 2012; 35: 574–80.
  18. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, Lowe LP, Coustan DR, Hod M, Oats JJ, Persson B, Trimble ER; HAPO Study Cooperative Research Group. Frequency of Gestational Diabetes Mellitus at Collaborating Centers Based on IADPSG Consensus Panel-Recommended Criteria: The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care* 2012; 35: 526–8.
  19. Khan KS, Syed AH, Hashmi FA, Rizvi JH: Relationship of fetal macrosomia to a 75 g glucose challenge test in nondiabetic pregnant women. *Aust N Z J Obstet Gynaecol* 1994; 34: 24–7.
  20. Shirazian N, Mahboubi M, Emdadi R, Yousefi-Nooraie R, Fazel-Sarjuei Z, Sedighpour N, Fadaki SF, Emami P, Hematyar M, Rahimi N, Mozaffari-Kermani R. Comparison of different diagnostic criteria for gestational diabetes mellitus based on the 75-g oral glucose tolerance test: a cohort study. *Endocr Pract* 2008; 14: 312–7.
  21. Sugaya A, Sugiyama T, Nagata M, Toyoda N. Comparison of the validity of the criteria for gestational diabetes mellitus by WHO and by the Japan Society of Obstetrics and Gynecology by the outcomes of pregnancy. *Diabetes Res Clin Pract* 2000; 50: 57–63.
  22. Dargham SR, Shewehy AE, Dakrouy Y, Kilpatrick ES, Atkin SL. Prediabetes and diabetes in a cohort of Qatari women screened for polycystic ovary syndrome. *Scientific Reports* 2018; 8: 3619.
  23. Christos PJ, Chemaitelly H, Abu-Raddad LJ, Ali Zirir M, Deleu D, Mushlin AI. Prevention of type II diabetes mellitus in Qatar: Who is at risk? *Qatar Med J* 2014; 2014: 70–81.
  24. Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, Lowe LP, Trimble ER, Coustan DR, Hadden DR, Persson B, Hod M, Oats JJ; HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome Study. *Diabetes Care* 2012; 35: 780–6.
  25. Alemu BT, Olayinka O, Baydoun HA. Neonatal hypoglycemia in diabetic mothers: A systematic review. *Curr Pediatr Res* 2017; 21: 42–53.
  26. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TR, Trimble ER, Coustan DR, Hadden DR, Hod M, Oats JJ, Persson B; HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care* 2012; 35: 574–80.
  27. González-Quintero VH, Istwan NB, Rhea DJ, Rodriguez LI, Cotter A, Carter J, Mueller A, Stanziano GJ. The impact of glycemic control on neonatal outcome in singleton pregnancies complicated by gestational diabetes. *Diabetes Care* 2007; 30: 467–70.
  28. Assaf-Balut C, Familiar C, García de la Torre N, Rubio MA, Bordiú E, Del Valle L, Lara M, Ruiz T, Ortolá A, Crespo I, Duran A, Herraiz MA, Izquierdo N, Perez N, Torrejon MJ, Runkle I, Montañez C, Calle-Pascual AL. Gestational diabetes mellitus treatment reduces obesity-induced adverse pregnancy and neonatal outcomes: the St. Carlos gestational study. *BMJ Open Diabetes Res Care* 2016; 20; 4(1): e000314.

29. Silva AL, Amaral AR, Oliveira DS, Martins L, Silva MR, Silva JC. Neonatal outcomes according to different therapies for gestational diabetes mellitus. *J Pediatr (Rio J)* 2017; 93: 87-93.
30. Garcia-Patterson A, Aulinas A, María MÁ, Ubeda J, Orellana I, Ginovart G, Adelantado JM, de Leiva A, Corcoy R. Maternal body mass index is a predictor of neonatal hypoglycemia in gestational diabetes mellitus. *J Clin Endocrinol Metab* 2012; 97: 1623-8.
31. Sreelakshmi PR, Nair S, Soman B, Alex R, Vijayakumar K, Kutty VR. Maternal and neonatal outcomes of gestational diabetes: A retrospective cohort study from Southern India. *J Family Med Prim Care* 2015; 4: 395-8.
32. Prakash GT, Das AK, Habeebullah S, Bhat V, Shamanna SB. Maternal and Neonatal Outcome in Mothers with Gestational Diabetes Mellitus. *Indian J Endocrinol Metab* 2017; 21: 854-8
33. Langer O, Yogev Y, Most O, Xenakis EM. Gestational diabetes: the consequences of not treating. *Am. J. Obstet. Gynecol* 2005; 192: 989-97.
34. Aris IM, Soh SE, Tint MT, Liang S, Chinnadurai A, Saw SM, Rajadurai VS, Kwek K, Meaney MJ, Godfrey KM, Gluckman PD, Yap FK, Chong YS, Lee YS. Effect of maternal glycemia on neonatal adiposity in a multiethnic Asian birth cohort. *J Clin Endocrinol Metab* 2014; 99: 240-7.
35. Shen S, Lu J, Zhang L, He J, Li W, Chen N, Wen X, Xiao W, Yuan M, Qiu L, Cheng KK, Xia H, Mol BWJ, Qiu X. Single Fasting Plasma Glucose Versus 75-g Oral Glucose-Tolerance Test in Prediction of Adverse Perinatal Outcomes: A Cohort Study. *EBioMedicine* 2017; 16: 284-91.
36. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. *Ann Nutr Metab* 2015; 66 (Suppl. 2): 14-20.
37. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005; 352: 2477-86.
38. Brook T Alemu, Olaniyi Olayinka, Hind A Baydoun, Matthew Hoch, Muge Akpınar Elci. Neonatal hypoglycemia in diabetic mothers: A systematic review. *Curr Pediatr Res* 2017; 21: 42-53.
39. Flores-le Roux JA, Sagarra E, Benaiges D, Hernandez-Rivas E, Chillaron JJ, Puig de Dou J, Mur A, Lopez-Vilchez MA, Pedro-Botet J. A prospective evaluation of neonatal hypoglycaemia in infants of women with gestational diabetes mellitus. *Diabetes Res Clin Pract* 2012; 97: 217-22.
40. Garcia-Patterson A, Aulinas A, María MÁ, Ubeda J, Orellana I, Ginovart G, Adelantado JM, de Leiva A, Corcoy R. Maternal body mass index is a predictor of neonatal hypoglycemia in gestational diabetes mellitus. *J Clin Endocrinol Metab* 2012; 97: 1623-8.
41. Tundidor D, García-Patterson A, María MA, Ubeda J, Ginovart G, Adelantado JM, de Leiva A, Corcoy R. Perinatal maternal and neonatal outcomes in women with gestational diabetes mellitus according to fetal sex. *Gend Med* 2012; 9: 411-7.
42. Mills JL. Malformations in infants of diabetic mothers. *Teratology* 25:385-94. 1982. *Birth Defects Res A Clin Mol Teratol* 2010; 88: 769-78.
43. Mitchell SC, Sellmann AH, Westphal MC, Park J. Etiologic correlates in a study of congenital heart disease in 56,109 births. *Am J Cardiol* 1971; 28: 653-7.
44. Kucera J. Rate and type of congenital anomalies among offspring of diabetic women. *J Reprod Med* 1971; 7: 73-82.

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