

An Observational Study of Maternal Hypoglycemia in Pregnancy

Inna Bleicher^{1,2}, Sharon Einav^{3,4}, Revital Perlov Gavze⁵, Liat Lev Shalem⁵, Rami Sammour^{1,2}

¹Department of Obstetrics and Gynecology, Bnai -Zion Medical Center, Haifa, Israel; ²The Ruth and Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel; ³Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; ⁴Hod HaSharon Maccabi Healthcare Services, Hod Hasharon, Israel; ⁵Medical Division, Maccabi Healthcare Services, Tel Aviv, Israel

Correspondence: Inna Bleicher, Department of Obstetrics and Gynecology, Bnai -Zion Medical Center, Haifa, Israel, Email innableicher@gmail.com

Background: Hypoglycemia in pregnancy is relatively understudied, with conflicting evidence suggesting either outcomes similar to normal oral glucose tolerance test (OGTT) or associations with poor neonatal outcomes. Maternal glucose crosses the placenta, thus maternal hypoglycemia may affect the fetus.

Objective: This study aimed to evaluate the association between maternal hypoglycemia and neonatal birth weight, specifically the risk of small-for-gestational-age (SGA) neonates, and to examine maternal metabolic outcomes in comparison to normoglycemic and hyperglycemic individuals.

Study Design: This retrospective cohort study included 39,306 primiparous individuals aged 18–50 years. Participants were classified as hypoglycemic (glucose <70 mg/dL) hyperglycemic (≥ 1 abnormal OGTT value), or normoglycemic. The primary outcome was the rate of SGA (<10th percentile) and large-for-gestational-age (LGA, >90th percentile) neonates. Secondary outcomes included maternal hypertensive disorders, gestational diabetes requiring treatment (GDMA2), and long-term risk of diabetes mellitus (DM).

Results: Among the cohort, 16,062 (40.9%) were hypoglycemic, 8543 (21.7%) were hyperglycemic, and 14,701 (37.4%) were normoglycemic. Compared to normoglycemic individuals, hypoglycemia was associated with an increased likelihood of SGA (OR 1.2, 95% CI 1.1–1.4), particularly in the second and third trimesters. Hyperglycemia was associated with an increased likelihood of LGA (OR 1.2, 95% CI 1.1–1.4). Hypoglycemia was also linked to a higher prevalence of gestational diabetes (GDMA2) and dysglycemia during pregnancy, yet a lower likelihood of developing DM later in life compared to hyperglycemic individuals.

Conclusion: Maternal hypoglycemia during pregnancy is associated with an increased risk of SGA neonates and may serve as an early marker of underlying glucose dysregulation. Given these findings, repeated glucose monitoring and closer follow-up for individuals with hypoglycemia may be warranted. Future research should investigate long-term neonatal and maternal metabolic outcomes to refine clinical management strategies for hypoglycemia in pregnancy.

Plain Language Summary: High blood sugar in pregnancy has been widely studied, but much less is known about the effects of low blood sugar. Some pregnant individuals have very low glucose values on routine screening tests. We wanted to understand whether these low values are linked to problems for the baby or to later health issues for the mother.

We analysed electronic medical records from almost 40,000 individuals in their first pregnancy who were insured by a large health organisation in Israel. We divided them into three groups according to their glucose test results in pregnancy: low, normal, or high. We then examined birth weight, pregnancy complications, and the risk of diabetes later in life.

We found that low glucose values in the second and third trimesters were associated with a higher risk of giving birth to a baby who was smaller than expected for gestational age. Mothers with low glucose values were also more likely to have other glucose abnormalities during pregnancy and to need treatment for gestational diabetes. However, compared with mothers who had high glucose values, they were less likely to be diagnosed with diabetes in the years after pregnancy. We did not observe major differences in the babies' health during the first year of life.

These findings suggest that low glucose values in pregnancy should not be considered reassuring. Instead, they may serve as an early marker of disturbed glucose regulation and support closer monitoring and follow up.

Keywords: hypoglycemia, small for gestational age, gestational diabetes, diabetes mellitus

Introduction

Gestational diabetes mellitus (GDM) is a common pregnancy complication, affecting approximately 15% of pregnant individuals globally.¹ GDM poses significant short- and long-term health risks for both the mother and the offspring, emphasizing the importance of early detection and management. In the short term, GDM is associated with maternal and fetal complications such as macrosomia (birth weight >4500 grams), large-for-gestational-age (LGA) infants, increased rates of operative vaginal deliveries and cesarean sections, birth trauma, severe perineal tears, preeclampsia, polyhydramnios, and intrauterine fetal demise. Long-term complications include a heightened risk of metabolic syndrome, cardiovascular disease, and type 2 diabetes mellitus for both mother and child.^{2–6}

The American College of Obstetricians and Gynecologists (ACOG) outlines that GDM diagnosis involves either a one-step or two-step process, often requiring at least two abnormal glucose values, though a single abnormal value may suffice in specific circumstances. “Abnormal values” are predominantly defined as elevated glucose levels.⁷

Hypoglycemia, defined as plasma glucose levels below 54–70 mg/dL, is a less frequently studied condition. Its implications, particularly in the context of the glucose challenge test (GCT) and oral glucose tolerance test (OGTT), remain a subject of debate. Some studies suggest that individuals with normal OGTT results exhibit comparable maternal and neonatal outcomes to those with hypoglycemia during OGTT. Other studies report a higher prevalence of pathological glucose patterns on self-monitoring, an increased prevalence low-birth-weight (<2500 grams), and a higher likelihood of subsequent GDM diagnosis in individuals with hypoglycemia during OGTT.^{8–10}

Given that maternal glucose diffuses to the fetus, maternal hypoglycemia could induce fetal hypoglycemia, potentially leading to fetal hypoxia and suboptimal growth. These findings underscore the need for a nuanced understanding of glucose abnormalities during pregnancy and their implications for maternal and neonatal health.¹¹

However, important knowledge gaps remain. Available studies are largely single-center, use heterogeneous hypoglycemia thresholds and testing strategies, and have limited ability to examine whether the timing of hypoglycemia during pregnancy modifies fetal growth risk. In addition, maternal metabolic outcomes beyond pregnancy, including subsequent diabetes risk, have rarely been evaluated in individuals with hypoglycemia detected on screening or diagnostic glucose testing.

The current study aimed to assess the rate of small-for-gestational-age (SGA) and large for gestational age (LGA) neonates among individuals with hyperglycemia, hypoglycemia and normoglycemia. We hypothesized that maternal hypoglycemia will be associated with an increased risk of small-for-gestational-age (SGA) just as hyperglycemia is associated with large for gestational age (LGA) neonates, in addition to pathological maternal metabolic outcomes and neonatal complications, when compared to normoglycemic individuals.

Methods

Study Design

This retrospective analysis of data from electronic medical records of Maccabi Healthcare Services (January 2000–December 2022) is reported according to the Reporting of Studies Conducted Using Observational Routinely Collected Data recommendations.¹²

Setting

The Maccabi Health Service (MHS) is the second-largest health maintenance organization (HMO) in Israel. Founded in 1940, it currently covers approximately 2.4 million insurees. Like all HMOs in the country, the MHS operates according to the guidelines of the national insurance law. The national health insurance law ensures that all residents of the country are entitled to a basket of healthcare services predetermined by a national committee. The costs of all pregnant individuals are mandatorily covered, and this population undergoes scheduled follow-up and testing. Medical treatment follows national guidelines which are written and updated periodically by the Israeli society of obstetrics and gynecology according to international guidelines. Follow-ups and tests are

routinely recorded in a standard electronic medical record (EMR). GCT and OGTT are performed according to ACOG recommendations, usually during the second trimester, between 24–28 gestational weeks.

Participants

The MHS database was used to identify those fulfilling the following criteria: Primiparous individuals, aged 18–50 years at the time of their last menstrual period, with a 100-gram oral glucose tolerance test (OGTT) results available, and a live birth. We also included patients with a 50-gram glucose challenge test (GCT) result <70 mg/dl, even if OGTT results were not available. Excluded were individuals with multiple gestation and those with missing data of neonatal outcomes or birthweight. Data were extracted up to a year after delivery.

Variables

The primary study outcome was the rate of large for gestation (LGA) or small for gestation (SGA) neonates. We defined LGA as birthweight >90th centile and SGA as birthweight <10th centile according to local birth charts.¹³ Individuals were classified as hyperglycemic if they had one or more elevated glucose level, as hypoglycemic if they had any glucose levels <70 mg/dl (with or without hyperglycemia) or as normoglycemic.⁷ Analysis was performed according to the trimester during which the pathological glucose level was measured. Since there is no standard definition for GDM, we chose to use the conservative definition of a single pathological value.⁷

The secondary study outcomes were the rates of complications (hypertensive disorder, DM later in life) among individuals with hypoglycemia as compared to those with normoglycemia, and whether these individuals with hypoglycemia were classified as dysglycemic (ie. defined as the presence of any ICD-10 diagnosis related to abnormal glucose metabolism recorded in the patient's medical chart; the diagnosis was made and documented by the treating physician during the index pregnancy) and required glucose lowering agents. We therefore also collected data on maternal demographics (maternal age at diagnosis, socio-economic status) and co-morbidities (smoking, body mass index [BMI]), the details of the current pregnancy (eg. maternal fetal medicine clinic follow-up, gestational age at diagnosis, glucose test results, gestational age at delivery), pregnancy complications (hypertensive disorders, diagnosis of GDMA1 and GDMA2), medical treatment for GDM and on later presentation of diabetes mellitus (DM according to the diabetes registry).

A list of codes used to identify the variables is provided in [Supplementary Table 1](#).

We also collected data on neonatal outcomes (birthweight, jaundice, hypoglycemia, rates of referral to a pediatrician or the department of emergency medicine during the first year of life, and failure to thrive [FTT]) and data on maternal follow up and outcomes (number of obstetrical medical visits, ultrasound examinations, referrals to the department of emergency medicine, and hospitalizations).

Data Sources/Measurement

All the data were extracted by MHS data analysts from the EMRs of relevant patients identified in the MHS database. All MHS tests are sent to standardized ISO-accredited central laboratories and results are sent electronically directly to the treating clinicians as well as being automatically documented in the EMRs. Measurements were unrelated to the study and were performed by independent clinicians and laboratory workers.

Bias

Selection bias is less likely given that MHS is the second-largest HMO and covers almost a third of the population in the country. Self-selection for testing is always a possibility despite full coverage of costs. Measurement bias is not likely given the rigorous standards upheld by the central MHS laboratories. Some doctors may have failed to document the presence of diabetes in the list of diagnoses. We overcame this issue by classifying patients according to their blood test results rather than through these lists.

Study Size

Study power was not calculated since this study covered the full database population rather than a sample.

Quantitative Variables

We studied age both as a continuous variable and as age above and below 35 years, due to the American Diabetes Association recommendation to screen for DM at this age in populations at risk.¹⁴ Blood pressure was classified according to the American Heart Association classification of hypertension.¹⁵ Neonatal weight categories and LGA and SGA were defined as commonly accepted.

Statistical methods

Missingness is reported. Categorical data were reported as the number (%) and compared using the Chi-square test. Continuous variables were reported as mean $\pm$ SD and median [Interquartile Range (Q1-Q3)]. Between-group comparisons were performed using analysis of variance (ANOVA) for normally distributed data and the Kruskal–Wallis test for non-parametric data. Logistic regression analysis was used to examine neonatal and maternal outcomes. All models were adjusted for maternal age at diagnosis, dysglycemia and GDMA2 unless GDMA2 was studied as an outcome. Models studying GDMA2 as an outcome were adjusted only for maternal age at diagnosis and dysglycemia. Models studying dysglycemia as an outcome were adjusted for maternal age at diagnosis and GDMA2. All data were analyzed using SPSS version 29 (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp). P-values less than 0.05 were considered significant.

Data Access and Cleaning Methods

MHS provides data analysts and statistical support. Aggregate data are provided to the researchers following data cleaning. Data cleaning included the following: OGTT with the value of “0” were considered missing, illogical neonatal weights (eg. 6666, 38). All analyses are performed by the support team as per request.

Linkage

Maternal and neonatal files were linked (person level) across a single data base using IDs with a proprietary code unique to the MHS.

Results

Participants

Overall, 169,346 potentially eligible primiparous individuals aged 18–50 years at the time of their last menstrual period with a pregnancy resulting in a live birth were identified in the MHS database. After excluding individuals with incomplete 100-gram oral glucose tolerance test (OGTT) and adding individuals who had hypoglycemic value (<70 mg/dl) in their 50-gram glucose challenge test (GCT), there were 47,086 eligible individuals. After further exclusion for multiple gestation and missing data regarding neonatal outcome or neonatal weight, the final study cohort included 39,306 individuals (Figure 1).

Missingness

Variables with the greatest amount of missing data were BMI in early pregnancy (84%), BMI at delivery (90%), weight in early pregnancy (60%), weight at delivery (53%) and fasting glucose in early pregnancy (50%).

Descriptive Data

The average maternal age at the time of diagnosis ranged between 28–31 years regardless of trimester of diagnosis. Diagnostic tests were performed during first, second and third trimester at an average of 9, 25 and 32 weeks of gestation, respectively. Most individuals were diagnosed during the second trimester of pregnancy. Additional maternal and neonatal characteristics are presented in Table 1.

Outcome Data

Overall, 8543 patients had hyperglycemia, 16,062 had hypoglycemia and 14,701 were normoglycemic.

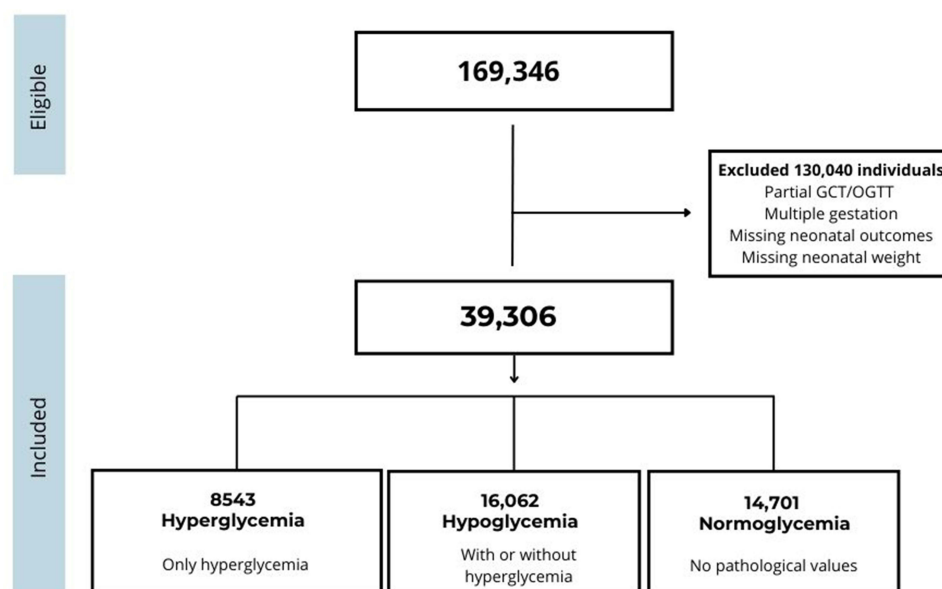


Figure 1 Inclusion exclusion flow chart.

Main Results

When comparing patients with hyperglycemia to normoglycemia in the second trimester, the likelihood of SGA <10 centile was 1.2 (95% CI 1.1–1.4), and the likelihood of SGA <1 centile was 3.5 (95% CI 1.6–7.8). This difference was not apparent in the third trimester.

When comparing patients with hypoglycemia to normoglycemia, the likelihood of SGA <10 centile was 1.2 (95% CI 1.1–1.4) in both the second and the third trimester, and the likelihood of SGA <1 centile was 2.5 (1.1–5.3) in the third trimester only. (Table 2). Neonatal follow-up during the first year of life after maternal hyperglycemia, hypoglycemia and normoglycemia is presented in [Supplementary Table 2](#) per trimester of diagnosis.

Compared to individuals with normoglycemia the likelihood of hypertensive disorder was increased in both hyper- and hypoglycemia. However, the number of patients in each group was very small. Compared to individuals with normoglycemia, individuals with hypoglycemia were less likely than individuals with hyperglycemia to be diagnosed with DM later in life. Compared to individuals with normoglycemia, the likelihood of diagnosis of dysglycemia during pregnancy (had ICD code for gestational diabetes in their medical chart) was also lower in individuals with hypoglycemia versus hyperglycemia. Although many hypoglycemic patients received treatment with glucose lowering agents (GDMA2), the adjusted likelihood of such treatment was lower in individuals with hypoglycemia versus hyperglycemia when compared to normoglycemia. (Table 3)

Utilization of obstetric services among patients with hyperglycemia, hypoglycemia and normoglycemia per trimester of diagnosis is presented in [Supplementary Table 3](#).

Discussion

Principal Findings

In this observational study of nearly 40,000 pregnant individuals who underwent either a GCT or an OGTT, the likelihood of SGA neonates was higher among those with hypoglycemia than those with normoglycemia. This association was most pronounced in the second and third trimesters of pregnancy. However, neonatal follow-up revealed no clinically significant differences in the studied variables within the first year of life.

Regarding maternal outcomes, the prevalence of hypertensive disorders was slightly higher in individuals with either hyperglycemia or hypoglycemia versus normoglycemia, although the difference appeared negligible. As expected, individuals in hyperglycemia group had a higher prevalence of GDMA2, more individuals were diagnosed with

Table 1 Population Characteristics

	First Trimester N=713				Second Trimester N=24,326				Third Trimester N=14,267			
	HYPER N=254	HYPO N=210	Normal N=249	p-value	HYPER N=5055	HYPO N=11218	Normal N=8053	p-value	HYPER N=3234	HYPO N=4634	Normal N=6399	p-value
GA at diagnosis (weeks)	9.5±1.9	9.7±1.8	9.6±1.8	0.534	25.9±2.0	25.5±1.9	25.9±1.9	<0.001	32.1±3.4	33.1±4.0	32.9±3.8	<0.001
Gestational age at delivery	38.5±1.8	39.0±1.4	39.0±1.9	0.002	38.7±1.7	39.1±1.7	39.0±1.7	<0.001	39.0±1.5	39.4±1.5	39.4±1.5	<0.001
Maternal age at diagnosis	31.2±5.5	31.1±4.9	29.8±4.7	0.002	30.8±5.4	28.6±5.3	29.6±5.2	<0.001	29.3±5.3	28.3±5.2	28.3±5.2	<0.001
Socio-economic status												
Low	36 (14.2)	28 (13.3)	30 (12.0)	0.642	694 (13.8)	2224 (19.8)	1211 (15.1)	<0.001	713 (22.1)	1077 (23.2)	1506 (23.6)	0.031
Intermediate	114 (45.1)	83 (39.5)	111 (44.6)		2379 (47.2)	4587 (40.9)	3565 (44.3)		1489 (46.1)	1977 (42.7)	2776 (43.4)	
High	103 (40.7)	99 (47.1)	108 (43.4)		1971 (39.1)	4394 (39.2)	3266 (40.6)		1026 (31.8)	1579 (34.1)	2107 (33.0)	
Smoking (Ever)	85 (33.5)	92 (43.8)	75 (30.1)	0.007	1777 (35.2)	3684 (32.8)	2451 (30.4)	<0.001	1087 (33.6)	1566 (33.8)	1844 (28.8)	<0.001
BMI (early in pregnancy)	28.1±6.3	28.6±6.6	26.8±5.9	0.171	27.5±6.2	24.3±5.4	25.6±5.6	<0.001	26.6±6.0	24.5±5.0	25.0±5.0	<0.001
Pregnancy weight gain(kg)	8.9±5.0	12.8±7.6	11.3±7.5	<0.001	10.3±5.7	13.0±6.5	12.4±6.3	<0.001	12.1±6.4	14.3±6.2	14.0±6.0	<0.001
First trimester FPG	100.5±7.5	98.3±8.1	97.3±7.8	0.002	89.7±8.4	85.2±7.5	87.6±7.1	<0.001	87.8±7.3	84.6±7.4	86.1±7.5	<0.001
Mean glucose at OGTT												
0'	98.6±7.8	92.2±8.0	88.4±4.8	<0.001	87.2±10.5	79.4±9.0	81.2±6.0	<0.001	86.4±10.5	76.6±8.7	80.0±6.0	<0.001
60 '	166.2±40.9	133.1±43.0	123.4±25.5	<0.001	188.5±28.3	150.6±36.7	142.0±23.9	<0.001	185.7±25.5	146.6±33.4	141±22.5	<0.001
120'	135.1±36.7	99.2±25.8	102.4±17.4	<0.001	159.4±30.0	116.2±29.1	118.3±19.4	<0.001	159.2±28.1	114.5±27.7	118.3±18.8	<0.001
180'	105.8±26.1	58.7±13.1	91.8±13.1	<0.001	114.7±27.3	60.1±19.4	97.5±16.5	<0.001	114.5±26.7	63.9±20.6	97.4±16.3	<0.001
50-gram GCT	149.9±33.3	125.7±34.0	124.3±28.4	<0.001	162.9±19.1	103.7±46.8	150.7±15.7	<0.001	146.8±26.0	119.7±34.3	126.1±27.7	<0.001

Note: Continuous variables are reported as Mean ±SD. Categorical variables are reported as N (%). Glucose levels are presented as mg/dl.

Abbreviations: GA, gestational age; FPG, fasting plasma glucose; GCT, glucose challenge test; BMI, body-mass index; OGTT, oral glucose tolerance test.

Table 2 Neonatal Outcomes

Trimester #	Parameter	HYPER	HYPO	Normal	Hyper vs. Normal OR [95% CI]	Hypo vs. Normal OR [95% CI]
First N=713	N	254	210	249	–	–
	SGA	20 (7.9)	11 (5.2)	23 (9.2)	0.8 [0.4–1.7]	0.5 [0.3–1.1]
	LGA	20 (7.9)	27 (12.9)	21 (8.4)	0.9 [0.5–1.8]	1.6 [0.9–2.9]
	Jaundice	6 (2.4)	9 (4.3)	3 (1.2)	2.5 [0.6–10.8]	3.9 [1.0–14.8]
	Admission to pediatrician during first year	110 (43.3)	108 (51.4)	107 (43.0)	1.4 [0.9–2.0]	1.6 [1.1–2.3]
	Failure to thrive	5 (2.0)	6 (2.9)	1 (0.4)	6.7 [0.8–60.3]	7.8 [0.9–65.9]
Second N=24,326	N	5055	11,218	8053	–	–
	Neonatal SGA below 10%	489 (9.7)	1174 (10.5)	701 (8.7)	1.2 [1.1–1.4]	1.2 [1.1–1.4]
	Neonatal LGA above 90%	419 (8.3)	713 (6.4)	725 (9.0)	0.8 [0.7–0.9]	0.7 [0.6–0.8]
	Jaundice	103 (2.0)	278 (2.5)	147 (1.8)	1.3 [1.0–1.7]	1.4 [1.1–1.7]
	Admission to pediatrician during first year	2722 (53.8)	7444 (66.4)	4503 (55.9)	1.3 [1.2–1.4]	1.6 [1.5–1.7]
	Failure to thrive	212 (4.2)	454 (4.0)	307 (3.8)	1.3 [1.1–1.5]	1.1 [0.9–1.3]
Third N=14,267	N	3234	4634	6399	–	–
	Neonatal SGA below 10%	213 (6.6)	306 (6.6)	354 (5.5)	1.1 [0.9–1.4]	1.2 [1.1–1.4]
	Neonatal LGA above 90%	551 (17.0)	776 (16.7)	1169 (18.3)	1.0 [0.9–1.1]	0.9 [0.8–1.0]
	Jaundice	70 (2.2)	114 (2.5)	164 (2.6)	0.8 [0.6–1.1]	0.9 [0.8–1.2]
	Admission to pediatrician during first year	1993 (61.6)	3339 (72.1)	4167 (65.1)	1.1 [1.0–1.2]	1.4 [1.3–1.5]
	Failure to thrive	101 (3.1)	154 (3.3)	204 (3.2)	1.1 [0.8–1.4]	1.1 [0.9–1.3]

Note: Models adjusted to maternal age at diagnosis, disglycemia and GDMA2 (when GDMA2 as outcome adjusted only to maternal age at diagnosis and disglycemia and when disglycemia as outcome adjusted only to maternal age at diagnosis and GDMA2).

Abbreviations: SGA, small for gestational age; LGA, large for gestational age.

Table 3 Maternal Outcomes

Trimester	Parameter	HYPER	HYPO	Normal	Hyper vs. Normal OR [95% CI]	Hypo vs. Normal OR [95% CI]
First N=713	N	254	210	249	–	–
	Diagnosis of DM	13 (5.1)	10 (4.8)	3 (1.2)	8.9 [2.6–30.7]	3.0 [0.8–11.5]
	Hypertensive disorders					
	Preeclampsia or BP of 80–89 or 130–139	13 (5.1)	10 (4.8)	3 (1.2)	4.1 [1.1–15.3]	3.7 [1.0–14.0]
	Preeclampsia or BP of 90–109 or 140–159	22 (8.7)	19 (9.0)	9 (3.6)	2.3 [1.0–5.4]	2.5 [1.1–5.7]
	Preeclampsia or BP of 110+ or 160+	0 (0.0)	1 (0.5)	3 (1.2)	–	0.2 [0.01–2.1]
	GDMA2*	80 (31.5)	28 (13.3)	8 (3.2)	8.3 [3.8–18.0]	3.4 [1.5–7.8]
Second N=24,326	Dysglycemia**	115 (45.3)	50 (23.8)	25 (10.0)	5.1 [3.1–8.4]	2.3 [1.4–3.9]
	N	5055	11,218	8053	–	–
	Diagnosis of DM	265 (5.2)	96 (0.9)	86 (1.1)	4.6 [3.6–6.0]	0.8 [0.6–1.1]
	Hypertensive disorders					
	Preeclampsia or BP of 80–89 or 130–139	229 (4.5)	288 (2.6)	265 (3.3)	1.3 [1.01–1.5]	0.8 [0.7–0.9]
	Preeclampsia or BP of 90–109 or 140–159	375 (7.4)	482 (4.3)	441 (5.5)	1.3 [1.1–1.5]	0.8 [0.7–0.9]
	Preeclampsia or BP of 110+ or 160+	89 (1.8)	113 (1.0)	99 (1.2)	1.4 [1.0–1.8]	0.8 [0.6–1.1]
	GDMA2*	624 (12.3)	157 (1.4)	19 (0.2)	41.6 [26.2–66.0]	6.3 [3.9–10.2]
	Dysglycemia **	1147 (22.7)	465 (4.1)	273 (3.4)	6.8 [5.9–7.9]	1.2 [1.1–1.4]

(Continued)

Table 3 (Continued).

Trimester	Parameter	HYPER	HYPO	Normal	Hyper vs. Normal OR [95% CI]	Hypo vs. Normal OR [95% CI]
Third N=14,267	N	3234	4634	6399	-	-
	Diagnosis of DM	120 (3.7)	34 (0.7)	65 (1.0)	3.7 [2.7–5.1]	0.7 [0.5–1.1]
	Hypertensive disorders					
	Preeclampsia or BP of 80–89 or 130–139	113 (3.5)	160 (3.5)	187 (2.9)	1.2 [0.9–1.5]	1.2 [0.9–1.5]
	Preeclampsia or BP of 90–109 or 140–159	197 (6.1)	258 (5.6)	303 (4.7)	1.3 [1.1–1.6]	1.2 [1.0–1.4]
	Preeclampsia or BP of 110+ or 160+	41 (1.3)	46 (1.0)	63 (1.0)	1.3 [0.8–1.9]	1.0 [0.7–1.5]
	GDMA2*	139 (4.3)	28 (0.6)	6 (0.1)	34.7 [15.2–79.3]	6.3 [2.6–15.2]
	Dysglycemia**	450 (13.9)	109 (2.4)	86 (1.3)	10.7 [8.5–13.6]	1.7 [1.3–2.3]

Notes: *GDMA2- gestational diabetes mellitus requiring pharmacological treatment. ** Dysglycemia: Defined as the presence of any ICD-10 diagnosis related to abnormal glucose metabolism recorded in the patient's medical chart. The diagnosis was made and documented by the treating physician during the index pregnancy. Models adjusted to maternal age at diagnosis, dysglycemia and GDMA2 (when GDMA2 as outcome adjusted only to maternal age at diagnosis and dysglycemia and when dysglycemia as outcome adjusted only to maternal age at diagnosis and GDMA2).

Abbreviations: DM, diabetes mellitus; BP, blood pressure.

dysglycemia during pregnancy (presence of ICD-10 diagnosis related to abnormal glucose metabolism recorded in the patient's medical chart by the treating physician during the index pregnancy) and more individuals were diagnosed with DM later in life, across all three trimesters. Interestingly, individuals with hypoglycemia also had a higher prevalence of GDMA2 and dysglycemia, albeit a similar prevalence of DM later in life, compared to individuals with normoglycemia. Due to the retrospective design of the study, the exact mechanism underlying this relationship remains unclear, but it is possible that patients with hypoglycemia underwent self-glucose monitoring more frequently, ultimately revealing previously undiagnosed diabetes requiring medical intervention. This finding supports the hypothesis that hypoglycemia following a glucose challenge may be an unrecognized marker of diabetes. Nevertheless, individuals with hypoglycemia versus hyperglycemia were less likely to be diagnosed with DM later in life. Additionally, while individuals with hyperglycemia had more frequent obstetric visits, those with hypoglycemia did not differ significantly in their visit frequency compared to normoglycemic individuals.

Results in Context of What is Known

Our study is unique in that it included a somewhat larger cohort than the largest study to date.¹⁶ Of previous studies evaluating hypoglycemia and pregnancy outcomes, two were conducted at the UK,^{10,17} one in China,¹⁸ one in the US¹⁶ and one in Israel.⁸ Four studies included data from a single medical center^{8,10,16,17} but only one included community-level data such as ours.¹⁸ Although two reports described maternal outcomes,^{16,17} these included pregnancy-related outcomes only, like hypertensive disorders, mode of delivery, postpartum hemorrhage and diagnosis of GDM. In the current study, we also examined the rate of diagnosis of DM later in life.

Our study included only individuals with a live birth as did prior studies.^{10,16–18} Our findings that hypoglycemia is associated with SGA were similar to several previous studies.^{10,16,18} Raviv et al found that the rate of SGA was similar once adjusted to maternal age, BMI, nulliparity, and any hypertensive disorder. However, they also stated that “it would be hard to ignore the differences in birthweight trends”.⁸

We found no clinically significant difference between hyperglycemic, hypoglycemic and normoglycemic individuals in either age or the rate of hypertensive disorders and therefore did not adjust for these variables, and the paucity of data regarding BMI in our database did not enable adjustment for this variable. Furthermore, our study population also differed from that of Raviv et al in maternal age (lower percent of individuals >35 years) and rate of nulliparity (100% vs. 30%).

Contrary to most prior studies,^{10,16,17} we limited the upper age of the included population to 50 years. Leng et al¹⁸ included only individuals aged less than 39 years. Our study included only individuals in their first pregnancy whereas the rest included both nulliparous and multiparous individuals.^{10,16–18} Across all studies, including ours, the criteria for inclusion in terms of glucose testing that were used for diagnosis and the cutoffs used for classification of abnormality

were inconsistent. For example, Ding et al used a cutoff of 82 mg/dl to define hypoglycemia during 50 g GCT,¹⁶ Nayak et al¹⁰ used 88.5 mg/dl, while we defined hypoglycemia less than 70 mg/dl on either 50 g GCT or 100OGTT.

Clinical Implications

In an ideal world, glucose tolerance testing would be conducted in the first trimester of pregnancy. Already at this early stage, more than half of individuals had abnormal glucose values. Individuals with a normal test during first trimester should repeat testing between 24–28 weeks where the highest insulin resistance, while individuals with abnormal glucose, high or low, should be requested to keep a glucose level diary for 1–2 weeks. Those with entirely normal values or sporadic hyperglycemia or hypoglycemia could probably continue intermittent self-glucose monitoring with appropriate lifestyle modification and regular maternal follow up. Those with abnormal values (> 15–20%) despite lifestyle modification, should be referred to maternal fetal medicine specialist clinics to consider further medical treatment. Glucose values should be addressed as a continuum, with pathology being recognized by consistently irregular findings on both sides of the normal spectrum.

Research Implications

Future studies should consider testing the feasibility of such an approach, should include highly granular, prospective data to enable controlling for potential confounders in a sufficiently large sample and should also include more outcome data on patient-centered outcomes.

Strengths and Limitations

Strengths of this study include its large, population-based sample size and the inclusion of long-term maternal outcomes—an aspect rarely addressed in prior work. The exclusive inclusion of primiparous individuals helps control for confounding due to obstetric history. Moreover, the use of real-world data from a national health maintenance organization (HMO) enhances generalizability.

The current study was retrospective, and therefore, despite the large sample size, determines association rather than causation. Although the MHS database covers almost one-third of the population in the country, this sample may still not represent the entire population, nor may it represent pregnant population elsewhere. The need to ensure generalizability requires further research. Our criteria for study inclusion were somewhat different from prior studies. However, the criteria for diagnosis of hypoglycemia during pregnancy are inconsistent across multiple papers. Due to limitations in file linkage, our data does not include in-hospital data such as complications during labor, mode of delivery, Apgar score, umbilical cord pH and neonatal intensive care unit admission.

Conclusion

Maternal hypoglycemia during pregnancy is associated with an increased risk of SGA neonates and may serve as an early marker of underlying glucose dysregulation. Given these findings, repeated glucose monitoring and closer follow-up for individuals with hypoglycemia may be warranted. Several considerations should guide interpretation of these findings. First, given the retrospective observational design, the associations observed cannot establish causality. Prospective validation is also required. Second, the definition of hypoglycemia in pregnancy may need further refinement.

Future studies should include prospective, trimester-specific assessment of glucose dynamics with standardized thresholds, incorporate detailed maternal metabolic phenotyping and nutritional data, and evaluate longer-term maternal and neonatal metabolic implications and outcomes. Such work is needed to inform evidence-based clinical management strategies.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT to enhance language and readability. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the final version of the paper.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to institutional and national data protection policies but may be made available from the corresponding author on reasonable request and subject to approval by Maccabi Healthcare Services.

Ethics Approval Statement

The study protocol was approved by the Maccabi Healthcare Services Institutional Review Board (0144-22-MHS) and adhered to the Declaration of Helsinki. All data were de-identified prior to analysis.

Patient Consent Statement

As this was a retrospective study using de-identified electronic health records, informed consent was waived by the institutional review board.

Author Contributions

Dr. Inna Bleicher: Conceptualization, Methodology, Investigation, Writing, Original Draft, Writing, Review and Editing. Revital Perlov Gavze: Methodology, Data Curation, Investigation, Supervision, Writing, Review and Editing. Liat Lev Shalem: Methodology, Data Curation, Investigation, Supervision, Writing, Review and Editing. Dr. Rami Sammour: Conceptualization, Methodology, Formal Analysis, Writing, Review and Editing. Prof. Einav Sharon: Writing, Original Draft, Writing, Review and Editing, Visualization. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This work was supported by Marom, the Maccabi Healthcare Services Research Program, Tel Aviv, Israel.

Disclosure

All authors declare no conflict of interest.

References

1. Rj G, Alsweiler J, Ae M, et al. diabetes mellitus: an overview of cochrane reviews (Review). *2020*. doi:10.1002/14651858.CD012394.pub3
2. Dudley DJ. Diabetic-associated stillbirth: incidence, pathophysiology, and prevention. *Obstet Gynecol Clin North Am.* **2007**;34(2):293–307. doi:10.1016/J.OGC.2007.03.001
3. Venkatesh KK, Lynch CD, Powe CE, et al. Risk of adverse pregnancy outcomes among pregnant individuals with gestational diabetes by race and ethnicity in the United States, 2014–2020. *JAMA.* **2022**;327(14):1356–1367. doi:10.1001/JAMA.2022.3189
4. Page KA, Romero A, Buchanan TA, Xiang AH. Gestational diabetes mellitus, maternal obesity, and adiposity in offspring. *J Pediatr.* **2014**;164(4):807. doi:10.1016/J.JPEDS.2013.11.063
5. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia.* **2019**;62(6):905–914. doi:10.1007/S00125-019-4840-2/FIGURES/3
6. Waters TP, Kim SY, Werner E, et al. Should women with gestational diabetes be screened at delivery hospitalization for type 2 diabetes? *Am J Obstet Gynecol.* **2020**;222(1):73.e1. doi:10.1016/J.AJOG.2019.07.035
7. Committee on Practice Bulletins—Obstetrics. Mellitus APBNo 190: GD. ACOG practice bulletin No. 190: gestational diabetes mellitus. *Obstet Gynecol.* **2018**;131(2):e49–e64. doi:10.1097/AOG.0000000000002501
8. Raviv S, Wilkof-Segev R, Maor-Sagie E, et al. Hypoglycemia during the oral glucose tolerance test in pregnancy—maternal characteristics and neonatal outcomes. *Int J Gynecol Obstet.* **2022**;158(3):585–591. doi:10.1002/IJGO.14037
9. Yuen L, Bontempo S, Wong VW, Russell H. Hypoglycaemia on an oral glucose tolerance test in pregnancy - Is it clinically significant? *Diabet Res Clin Pract.* **2019**;147:111–117. doi:10.1016/J.DIABRES.2018.11.018
10. Nayak AU, Vijay AMA, Indusekhar R, Kalidindi S, Katreddy VM, Varadhan L. Association of hypoglycaemia in screening oral glucose tolerance test in pregnancy with low birth weight fetus. *World J Diabetes.* **2019**;10(5):304–310. doi:10.4239/WJD.V10.I5.304
11. Illsley NP, Baumann MU. Human placental glucose transport in fetoplacental growth and metabolism. *Biochim Biophys Acta Mol Basis Dis.* **2020**;1866(2):165359. doi:10.1016/J.BBADDIS.2018.12.010
12. Benchimol EI, Smeeth L, Guttman A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med.* **2015**;12(10):e1001885. doi:10.1371/journal.pmed.1001885
13. Dollberg S, Haklai Z, Mimouni FB, Gorfain I, Gordon ES. Birthweight standards in the live-born population in Israel. *Isr Med Assoc J.* **2005**;7(5):311–314.

14. ElSayed NA, Aleppo G, Bannuru RR; American Diabetes Association Professional Practice Committee. 2. diagnosis and classification of diabetes: standards of care in Diabetes—2024. *Diabetes Care*. 2024;47(Suppl 1):S20–S42. doi:10.2337/dc24-S002
15. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Hypertension*. 2018;71(6):e13–e115. doi:10.1161/HYP.0000000000000065
16. Ding JJ, Lundsberg LS, Culhane JF, Patridge C, Milley L, Son M. The association between a low 50-gram, 1-hour glucose challenge test value and neonatal morbidity. *J Matern Fetal Neonatal Med*. 2023;36(2):2245527. doi:10.1080/14767058.2023.2245527
17. Blunt C, Mathew S, Mung SM, Krishnamurthy R, Jude EB. Hypoglycaemia following the 2-hour 75g OGTT in pregnancy - Investigating maternal and foetal outcomes. *Diabetes Metab Syndr*. 2024;18(3):102977. doi:10.1016/j.dsx.2024.102977
18. Leng J, Hay J, Liu G, et al. Small-for-gestational age and its association with maternal blood glucose, body mass index and stature: a perinatal cohort study among Chinese women. *BMJ Open*. 2016;6(9):e010984. doi:10.1136/bmjopen-2015-010984

Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-journal>