# Flat Oral Glucose Tolerance Test During Pregnancy: Maternal Characteristics and Risk for Adverse Outcomes

*Amir Naeh, Renana Wilkof-Segev, Anat Jaffe, Esther Maor-Sagie, Mordechai Hallak, and Rinat Gabbay-Benziv*

Flat oral glucose tolerance test (OGTT) curve is characterized by low glucose levels, seemingly nonresponsive to glucose load. Few studies have explored flat OGTT during pregnancy and have yielded conflicting results, some suggesting risk for fetal growth restriction. This study evaluated the characteristics and perinatal outcomes of women with a flat OGTT during pregnancy. We found that a flat OGTT curve occurs in younger, leaner pregnant women. Also, flat OGTT curve was significantly associated with a male fetus and higher levels of pregnancy-associated plasma protein A at the first-trimester screening. Although flat OGTT can possibly reflect some degree of hyperinsulinemia, it is generally not associated with adverse maternal or neonatal outcomes.

Gestational diabetes mellitus (GDM) complicates 3–8% of pregnancies and is associated with maternal and neonatal adverse outcomes (1–3). The American College of Obstetrics and Gynecology recommends universal GDM screening for all pregnant women with a nonfasting, 1-hour, 50-g glucose challenge test (GCT). Women who screen positive then have a diagnostic 100-g, 3-hour oral glucose tolerance test (OGTT) (4). GDM is classically diagnosed by two or more abnormal values on the OGTT or any value >200 mg/dL. Different cutoffs for the 3-hour OGTT have been proposed, with the Carpenter and Coustan thresholds commonly used (5). Recent evidence suggests that even a single abnormal value on the OGTT is associated with adverse perinatal outcomes and future maternal type 2 diabetes and therefore requires consideration during pregnancy (6).

The common glucose curve after the OGTT glucose challenge is monophasic: a relatively low fasting value, followed by rising glucose levels reflecting the glucose load, usually achieving a maximum value at the 1-hour mark and gradually decreasing through the 2- and 3-hour evaluations. "Flat OGTT" is characterized by a low glucose level throughout the OGTT that is seemingly nonresponsive to the 100-g glucose load. It was first described by Thaysen and Norgaard (7) in 1929 in a nonobstetric population and was found to be associated with obesity, malabsorption disorders, and endocrinological disorders, including hyperinsulinism, hypothyroidism, and hypoadrenalism (7–10).

Only a few studies have explored flat OGTT during pregnancy, yielding conflicting results, with some demonstrating higher risk for fetal growth restriction (FGR) (11,12) and others showing no difference in perinatal outcomes (13,14). Comparison of these studies is limited by differences in selected populations, testing protocols, and definition of flat OGTT.

In this study, we aimed to further evaluate the flat OGTT phenomenon during pregnancy to identify its prevalence, assess its maternal characteristics, and investigate its possible association with perinatal adverse outcomes.

## Research Design and Methods

### *Study Population and Data Retrieval*

This was a retrospective analysis of prospectively collected data on all women who delivered babies in one university-affiliated medical center between 1 January 2018 and 31 December 2019. We included all women who had an OGTT with available results. We excluded women with a previous diagnosis of type 2 diabetes, multiple gestations, preterm deliveries <34 weeks, or incomplete OGTT data

Department of Obstetrics and Gynecology, Hillel Yaffe Medical Center, Hadera, and the Rappaport Faculty of Medicine, Technion, Haifa, Israel

**Corresponding author:** Amir Naeh, amir_naeh@outlook.com

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or delivery outcomes. The study was approved by the local institutional review board (HYMC-20-0052). Because of the retrospective nature of the study, the requirement for informed consent was waived.

By convention and according to Israel Society of Obstetrics and Gynecology guidelines (15), all parturients are advised to have a fasting glucose test during the first trimester to exclude overt diabetes, followed by a GCT at 24–28 gestational weeks and an OGTT for women who screen positive with the GCT (>140 mg/dL). Women with diabetes risk factors (e.g., BMI >30 kg/m$^2$, previous GDM or macrosomia, or strong family history of type 2 diabetes [4]) are advised to have the OGTT directly instead of a GCT. Polyhydramnios and a fetus that is large for gestational age at the third trimester are considered relative indications for performing an OGTT for parturients with a normal GCT, depending on other maternal risk factors and physician discretion. Therefore, the study cohort consisted of parturients with *1*) an OGTT after abnormal GCT, *2*) a normal GCT and then an OGTT because of late indication for GDM, and *3*) results of an OGTT performed instead of a GCT because of risk factors. Note that in any case of material vomiting after an OGTT glucose load, it is customary to end the evaluation, and any results are considered invalid.

Maternal and neonatal data were retrieved from the center's computerized comprehensive perinatal database. OGTT values were presented by parturients or extracted from the national laboratory database on maternal admission to the hospital. Other maternal, perinatal, and neonatal data are documented prospectively on admission and immediately after delivery. Retrieved data included maternal characteristics (e.g., age, BMI, parity, and previous medical and obstetrics background). Pregnancy characteristics included pregnancy surveillance data and complications (e.g., hypertensive disorders and amniotic fluid disorders). Delivery outcomes included gestational age at delivery, need for induction, mode of delivery, and neonatal and maternal outcomes until discharge. Neonatal birth weight was presented as absolute and as percentiles according to sex-specific local growth curves (16).

### *Definitions*

A flat OGTT curve was defined as a fasting glucose <95 mg/dL with all of the three subsequent values <100 mg/dL, as previously described (9). According to this definition, all women with an OGTT were categorized to three groups: group 1–normal OGTT (excluding flat OGTT), group 2–abnormal OGTT (one or more abnormal values), and group 3–flat OGTT. Because one abnormal pathological value was previously found to be related to increased birth weight and adverse perinatal outcomes (6), we included those instances in the abnormal OGTT group.

Gestational age at delivery was determined by parturients' last menstrual period and verified by first-trimester ultrasound, when available.

### *Statistical Analysis*

Data analysis was performed using SPSS v. 21.0 software (SPSS, Inc., Chicago, IL). $P$ <0.05 was considered significant. Categorical data were analyzed using the Fisher exact test, and continuous variables were compared using the Kruskal-Wallis test as appropriate.

## Results

During the study period, there were 9,068 deliveries at our center. We excluded 203 women with multiple gestations and 169 pre-term deliveries (<34 weeks of gestation). A total of 2,085 patients had available OGTT results and entered analysis. Of these 2,085 OGTT results, 1,193 parturients (57.3%) had a normal OGTT, and 794 (38%) had an abnormal OGTT with at least one pathological value. Ninety-eight women (4.7%) had a flat OGTT curve. Average glucose levels during OGTT in the three study groups are shown in Figure 1.

### *Maternal Characteristics*

Maternal demographics of patients in the three study groups are presented in Table 1. Women in the flat OGTT group were significantly younger, with lower BMI. Interestingly, flat OGTT was more prevalent in pregnancies carrying a male fetus, and with higher pregnancy-associated plasma protein A (PAPP-A) values during first-trimester screening.

Indications for performing OGTT differed between the entire cohort and the study group (Table 2). For the entire cohort, more than half of the cohort (55.9%) underwent OGTT because of elevated GCT result. However, for the flat OGTT group, only a minority (14%) had increased GCT, and the majority (61.2%) had a direct OGTT instead of GCT based on background risk factors.

### *Perinatal Adverse Outcomes and Neonatal Complications*

Women in the flat OGTT group were less likely to undergo induction of labor and, overall, delivered at a more advanced gestational age (Table 3). There were no

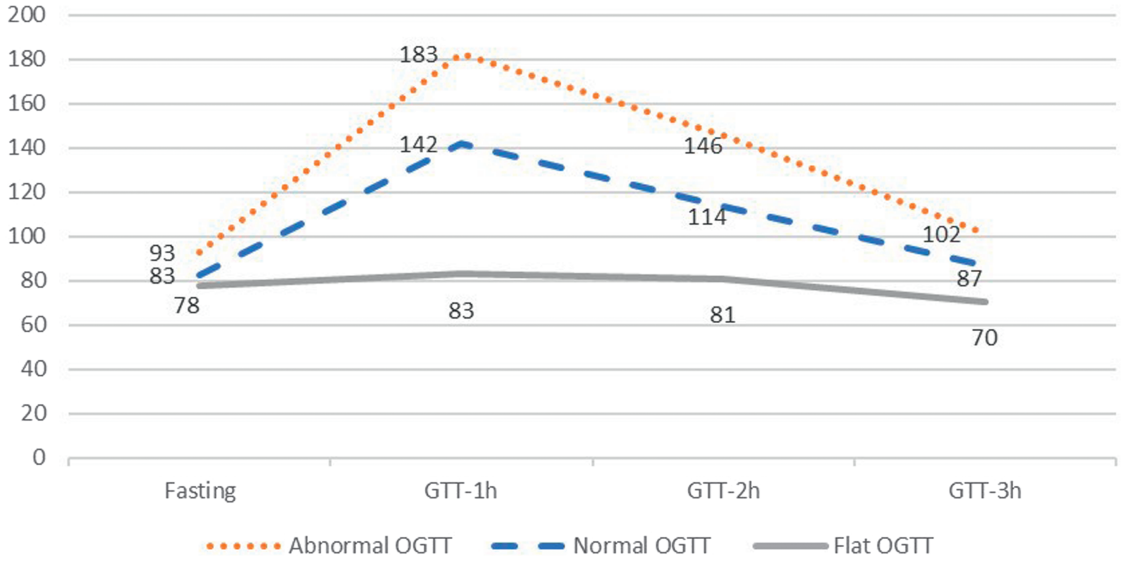


FIGURE 1 Average glucose levels (mg/dL) during OGTT in the three study groups. GTT, glucose tolerance test; h, hour(s).

differences in rates of cesarean delivery, instrumental delivery, or shoulder dystocia.

The average birth weight for the entire cohort was 3,350 g at 39 weeks plus 1 day gestation, corresponding to the 61.4 percentile using local growth curves (16). Neonates of women in the flat OGTT group were characterized by higher mean birth weight and a lower rate of being small for gestational age (SGA) (<10%). However, when adjusted to gestational age at delivery, no difference was found in birth weight percentiles.

There were no differences among the groups with regard to short-term neonatal outcomes, including neonatal pH, low 5-minute Apgar score, and admission to the neonatal intensive care unit (NICU).

Interestingly, women in the flat OGTT group demonstrated a trend toward a higher rate of postpartum hemorrhage, with a significantly greater rate of receiving a blood products transfusion in the peripartum period, and had significantly lower pre- and postpartum hemoglobin levels.

**TABLE 1** Demographic and Obstetrical Characteristics of Study Population

| | Group 1–Normal OGTT ($n$ = 1,193) | Group 2–Abnormal OGTT ($n$ = 794) | Group 3–Flat OGTT ($n$ = 98) | $P$ |
|---|---|---|---|---|
| Maternal age, years | 31.4 ± 5.4 | 32.3 ± 5.6 | 29.1 ± 5.3 | **<0.001** |
| Maternal age <20 years | 10 (0.8) | 8 (1) | 3 (3.1) | 0.1 |
| Maternal age >35 years | 344 (28.5) | 281 (34.9) | 19 (19.2) | **<0.001** |
| Maternal age >40 years | 96 (8) | 91 (11.5) | 2 (2) | **0.02** |
| BMI, kg/m$^2$ | 31 ± 5.7 | 31.7 ± 6 | 29.4 ± 5.9 | **0.02** |
| Nulliparity | 384 (32.2) | 285 (35.9) | 27 (27.6) | 0.1 |
| Bariatric surgery | 5 (0.4) | 0 (0) | 0 (0) | 0.1 |
| Previous cesarean delivery | 175 (14.5) | 131 (16.3) | 14 (14.1) | 0.5 |
| Chronic hypertension | 14 (1.2) | 16 (2) | 2 (2) | 0.3 |
| First trimester fasting glucose, mg/dL | 84.4 ± 7.9 | 92.3 ± 21.1 | 82.1 ± 10.3 | **<0.001** |
| First trimester PAPP-A, MoM | 1.14 ± 0.6 | 1.04 ± 0.6 | 1.25 ± 0.6 | **0.006** |

Categorical values are presented as $n$ (%) and continuous variables are presented as mean ± SD. Significant results ($P$ <0.05) are presented in bold. MoM, multiple of the median.

**TABLE 2** Indications for Undergoing OGTT in the Flat OGTT Group

| Indication for OGTT | Entire Cohort ($N$ = 2,085) | Flat OGTT ($n$ = 98) |
|---|---|---|
| Abnormal GCT* | 1,165 (55.9) | 14 (14.3) |
| Normal GCT and late indication for GDM† | 212 (10.2) | 24 (24.5) |
| OGTT instead of GCT due to risk factors‡ | 708 (33.9) | 60 (61.2) |

Data are $n$ (%). *GCT >140 mg/dL. †Late indications for performing OGTT after normal GCT include polyhydramnios or large-for-gestational-age fetus. ‡Risk factors regarded as indications for direct OGTT include previous GDM, previous macrosomia, strong family history of diabetes, and obesity.

## Discussion

In this study, we aimed to evaluate the prevalence and characteristics of parturients presenting with flat OGTT curve and investigate whether flat OGTT is associated with perinatal adverse outcomes.

We found a flat OGTT prevalence of 4.7% and that women with a flat OGTT curve were younger and leaner. Furthermore, flat OGTT was associated with male fetuses and with higher levels of first-trimester PAPP-A. Additionally, the neonates of women in the flat OGTT group were characterized by higher average birthweights, but exhibited no difference in birth weight percentile. Finally, a flat OGTT curve was not significantly associated with any other perinatal adverse outcomes except for a higher rate of blood products transfusion and lower pre- and postpartum hemoglobin levels.

During pregnancy, glucose is one of the principal nutrients supplied by the pregnant woman through the placental circulation to the fetus. Therefore, maternal alterations in glucose metabolism can potentially compromise fetal nutrition and predispose to abnormal fetal growth (17).

Previous studies have shown an association between low glucose levels (at different thresholds) in GCT and OGTT and adverse pregnancy outcomes, including delivery of an SGA neonate and higher rates of NICU admission (18–23). However, only a few studies have investigated flat OGTT during pregnancy and its association with perinatal adverse outcomes (11–14). Flat OGTT is a different clinical entity, representing not only low absolute glucose levels, but also the absence of an increase in blood glucose level after an OGTT glucose load.

Although the prevalence of flat OGTT in our cohort (4.7%) is similar to that found in previous studies (7,9,13), we assume it relates to both the characteristics of the population and the specific indication for OGTT. In our cohort, the majority of women in the flat OGTT group (61.2%) had an OGTT based on maternal risk factor and not because of an elevated GCT result (Table 2). It is possible that these women represent a subset of parturients who are at high risk for GDM but who do not have impaired glucose tolerance and actually represent the normal population. Still, almost 15% of the flat OGTT group had high glucose levels during GCT. The pathophysiology for this subset is not yet fully elucidated.

Previous results about perinatal outcomes in women with flat OGTT have been conflicting. Whereas some studies found an association between flat OGTT with FGR and SGA (11,12), others, like our study, found no difference in birth weight and SGA rate (13,14).

The difference among studies can be explained by several reasons. First, no universal definition for flat OGTT was established, with some studies defining flat OGTT according to the maximal increase in glucose levels compared with fasting levels (7,8,10), some by the difference between every two sequential evaluations (11), and others using an absolute cutoff for all four evaluations (9,14). In our study, we considered using the 10th-percentile cutoff for each of the four evaluated OGTT values (5) as the independent value; however, using this method would have maintained the increase in glucose levels after the glucose load (unlike a flat curve). Second, the evaluated population was different in size and characteristics among studies. Langer et al. (12) assessed 43 women at high risk for FGR (e.g., heavy smokers and those with previous SGA fetuses), whereas Valensise and Romanini (11) evaluated 192 women, including patients at high risk for SGA. To the best of our knowledge, our studay includes the largest unselected cohort size of women having an OGTT for an accepted indication. Finally, differences in testing protocols using 50- or 100-g OGTT glucose loads may also have influenced the results.

Interestingly, a flat OGTT curve was associated with having a male fetus. Previous studies have shown an association between male sex and altered glucose tolerance status, with a higher adjusted risk for large-for-gestational-age neonates, even after controlling for confounding variables (23–25). The cause for this association is not yet known and requires further study.

An association between high PAPP-A level and altered glucose tolerance has been described (26,27). PAPP-A is produced by the placenta during pregnancy and probably has a role in regulating glucose levels by cleaving insulin-like growth factor binding proteins and affecting their bioavailability (26,27).

**TABLE 3** Maternal and Neonatal Outcomes

| | Group 1–Normal OGTT ($n$ = 1,193) | Group 2–Abnormal OGTT ($n$ = 794) | Group 3–Flat OGTT ($n$ = 98) | $P$ |
|---|---|---|---|---|
| *Pregnancy and delivery outcomes* | | | | |
| Hypertensive disorder of pregnancy* | 75 (6.3) | 55 (6.9) | 7 (7.1) | 0.8 |
| Induction of labor (excluding elective cesarean) | 399 (40.1) | 304 (48.2) | 32 (39.5) | **0.005** |
| Gestational age at delivery, weeks | 39.2 ± 1.3 | 38.8 ± 1.2 | 39.4 ± 1.4 | **<0.001** |
| Instrumental delivery | 82 (6.9) | 47 (5.9) | 5 (5.1) | 0.6 |
| Cesarean delivery | 286 (24) | 216 (27.2) | 22 (22.4) | 0.2 |
| OASIS | 9 (0.8) | 12 (1.5) | 2 (2) | 0.1 |
| Shoulder dystocia | 19 (1.6) | 12 (1.5) | 3 (3.1) | 0.5 |
| Postpartum hemorrhage | 37 (3.1) | 33 (4.2) | 6 (6.1) | 0.1 |
| Blood products transfusion | 33 (2.8) | 22 (2.8) | 7 (7.1) | **0.04** |
| Hemoglobin, prepartum, g/dL | 11.9 ± 1.1 | 12 ± 1.1 | 11.7 ± 1.3 | **0.02** |
| Hemoglobin, postpartum, g/dL | 10.9 ± 1.4 | 11.1 ± 1.4 | 10.5 ± 1.6 | **0.02** |
| *Neonatal outcomes* | | | | |
| Male sex | 665 (55.7) | 400 (50.4) | 63 (64.3) | **0.007** |
| Birth weight, g | 3,382 ± 469 | 3,295 ± 484 | 3,400 ± 431 | **0.001** |
| Birth weight <2,500 g | 33 (2.8) | 43 (5.4) | 2 (2) | **0.006** |
| Birth weight >4,000 g | 120 (10.1) | 45 (5.6) | 7 (7.1) | **0.002** |
| Birth weight percentile† | 61.0 ± 26.2 | 62.0 ± 25.4 | 61.0 ± 25.9 | 0.936 |
| Birth weight <10th percentile | 48 (4) | 42 (5.3) | 0 (0) | **0.03** |
| Birth weight >90th percentile | 42 (15.2) | 31 (15.6) | 3 (13) | 0.949 |
| Neonatal pH | 7.29 | 7.28 | 7.29 | 0.6 |
| Perinatal death | 2 (0.2) | 3 (0.4) | 0 (0) | 0.5 |
| Admission to NICU | 31 (2.6) | 31 (3.9) | 4 (4.1) | 0.2 |
| 5-Minute Apgar score <8 | 5 (0.4) | 4 (0.5) | 0 (0) | 0.7 |

Categorical values are presented as $n$ (%), and continuous variables are presented as mean ± SD. Significant results ($P$ <0.05) are presented in bold. *Including gestational hypertension or preeclampsia. †Calculated according to sex-specific local growth curves (16). OASIS, obstetric anal sphincter injuries.

Neonates of women in the flat OGTT group were characterized by higher mean birth weight, but without a difference in birth weight percentiles. We assume that this finding was secondary to the fact that parturients in the flat OGTT group were less likely to undergo early induction of labor. Therefore, they delivered fetuses at a more advanced gestational age, and this was probably the cause for the higher birthweights.

The only adverse pregnancy outcomes found to be significant in the flat OGTT group were a higher rate of blood products transfusion and lower pre- and postpartum hemoglobin levels. Six of the seven women who received blood products had a postpartum hemorrhage, which was also found to occur at a higher rate in this group but did not reach statistical significance. Whether this was an incidental finding in a small cohort, secondary to a malabsorption disorder causing maternal iron deficiency anemia or represents a coagulability disorder secondary to hyperinsulinemic state (28) needs further research.

The exact pathophysiology for flat OGTT is unknown. The main suggested mechanisms are rapid removal of glucose from the bloodstream and poor absorption from the

gastrointestinal tract (8). The first mechanism can be caused by relative hyperinsulinemia—constantly higher physiological levels of insulin—causing administered glucose to be quickly absorbed into body tissues and therefore eliminating the monophasic glucose curve. Other causes include a lack of insulin antagonists, as in hypoadrenalism and hypothyroidism (10).

Poor absorption can be self-induced (e.g., if a patient avoids swallowing the glucose or vomits during OGTT) or can occur secondary to malabsorption disorders and gastric bypass procedures. Moreover, flat OGTT may represent a form of dumping syndrome, a state of rapid gastric emptying, in which the administration of glucose causes a shift of fluid from the intravascular component to the intestinal lumen, release of gastrointestinal and pancreatic hormones, and relative hypoglycemia (29). In our cohort, none of the parturients with flat OGTT had a history of bariatric surgery.

Our study's strengths include its large sample size—to the best of our knowledge, the largest yet to evaluate flat OGTT during pregnancy—and the ethnic diversity of the population admitted to and delivering in our institute. Also, our study was based on our computerized database, which is under constant, prospective, meticulous review by senior attending physicians. However, the study is not free of limitations. Restrictions included its retrospective design, limited cohort size, and lack of long-term results such as neonatal outcomes and maternal glucose status postpartum. Furthermore, although asked at data entry, the retrospective nature of the study cannot eliminate maternal vomiting or other failure to ingest the OGTT glucose load.

In conclusion, our study demonstrates that a flat OGTT curve is associated with a younger, leaner obstetrical population. Although flat OGTT can possibly reflect some degree of hyperinsulinemia, it is generally not associated with adverse maternal or neonatal outcomes. Further studies are needed to investigate the exact mechanism for this finding and to evaluate long-term maternal and neonatal outcomes.

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## DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

## AUTHOR CONTRIBUTIONS

A.N. contributed to the design of the study and interpretation of data and wrote and revised the manuscript. R.W.-S. and M.H. contributed to interpretation of data and revision of the manuscript. A.J. and E.M.-S. contributed to the design of the study, interpretation of data, and revision of the manuscript. R.G.-B. contributed to the design of the study, performed the statistical analysis, and revised the manuscript. A.N. and R.G.-B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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