Abnormal preconception oral glucose tolerance test predicts an unfavorable pregnancy outcome after an in vitro fertilization cycle

Hsiao-Jui Wei, M.D.,[a,b] *Robert Young, M.D.,*[b] *I-Li Kuo, M.D.,*[b] *Chian-Mey Liaw, B.S.,*[b] *Han-Sun Chiang, M.D., Ph.D.,*[a,c] *and Ching-Ying Yeh, Ph.D.*[a]

[a] Graduate Institute of Medical Science, Taipei Medical University; [b] Infertility Center, Taiwan Adventist Hospital; and [c] College of Medicine, Fu Jen Catholic University, Taipei, Taiwan

Objective: To determine the relationship between the 75-g oral glucose tolerance test and pregnancy outcome after women's first IVF cycle.
Design: Prospective study.
Setting: Infertility center at a private tertiary hospital in Taiwan.
Patient(s): All 280 patients who went through their initial IVF cycle at the hospital between January 2004 and April 2005 were included in the study.
Intervention(s): Two hundred eighty patients underwent an oral glucose tolerance test before entering an IVF cycle; all pregnancy outcomes and pregnancy complications were recorded.
Main Outcome Measure(s): The relationships between glycemic parameters and insulin resistance and IVF pregnancy outcome were determined. Linear regression between birth weight and levels of preconception fasting insulin, 2-hour glucose, and 2-hour insulin was performed.
Result(s): One hundred twenty patients conceived after their initial IVF cycle. Twenty-five of 89 ongoing pregnancies had various complications. The most common pregnancy complication was preterm birth (n = 11). These patients had higher body mass index (23.46 vs. 20.97 kg/m^2); higher fasting glucose (107.36 vs. 95.14 mg/dL), fasting insulin (10.55 vs. 6.20 μIU/mL), and 2-hour glucose (120.55 vs. 99.97 mg/dL) levels; and higher homeostatic model assessment of insulin resistance (3.43 vs. 1.45) than did patients with full-term pregnancies. Linear regression between birth weight and the fasting glucose level and between birth weight and the homeostatic model assessment of insulin resistance had positive correlations.
Conclusion(s): Before proceeding with IVF, preconception oral glucose tolerance testing is suggested, especially in patients with higher body mass index, to help identify groups who are at high risk for preterm birth. (Fertil Steril® 2008;90:613–8. ©2008 by American Society for Reproductive Medicine.)

Key Words: Infertility, oral glucose tolerance test, impaired glucose tolerance, diabetes mellitus, preterm labor

Hyperinsulinemia is related to the development of type 2 diabetes mellitus (DM). Patients with hyperinsulinemia have a higher risk for gestational diabetes mellitus (GDM), which predisposes to many pregnancy complications (1). Extensive studies have documented the impact of impaired glucose tolerance (IGT) on pregnancy, which increases the risk of other pregnancy complications, such as pregnancy-induced hypertension, fetal anomalies, and placental abruption (2–8), but many studies have only selected patients with polycystic ovarian syndrome or patients with difficulty in conceiving, and most studies performed only gestational, not preconception, glucose tolerance testing.

There are methodologic hurdles to overcome in identifying the preconception risk between glucose intolerance or hyperinsulinemia and preterm birth, such as the difficulty in screening the entire group of pregnant patients, inclusion of those patients who may want to try but cannot get pregnant, and inclusion of those patients who may attempt to become pregnant for a long period of time but who are found to have other confounding factors that interfere with the study. Patients enrolled in IVF cycles are ideal for testing the relationship between preconception disturbances in glucose homeostasis and pregnancy outcome. Indeed, there is a high pregnancy rate within a short period of time after the oral glucose tolerance test (OGTT).

This study may be one of the few attempts to correlate preconception 75-g glucose tolerance data in IVF patients who have adverse pregnancy outcomes (9, 10). We attempted to determine whether the characteristics of our patients, who are generally slim (an average body mass index [BMI] of 21.2 kg/m^2) and have IGT, can affect the pregnancy outcome (11, 12).

MATERIALS AND METHODS

Patients

We studied 280 patients between January 2004 and April 2005 who went through their initial IVF cycle at the Taiwan

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Reprint requests: Ching-Ying Yeh, Ph.D., Graduate Institute of Medical Science, Taipei Medical University, No. 250, Wusing Street, Taipei, Taiwan, 100 (FAX: 886-2-27384831; E-mail: yehcy@tmu.edu.tw).

Adventist Hospital (Taipei, Taiwan). All patients whose IVF cycles resulted in egg retrieval and embryo transfer were included in the analysis. This study was approved and conducted according to the guidelines of the Taiwan Adventist Hospital Investigational Review Board. All subjects signed their informed consent before the study.

Figure 1 shows the flow chart for IVF patients in this study, along with pregnancy results and outcomes.

Study Protocol

Before beginning the IVF cycle, every patient underwent hormone assays (which included FSH, LH, E_2, PRL, T, and androstenedione levels) and a 75-g OGTT on the 2nd or 3rd day of the spontaneous (n = 266 women) or induced (n = 14 women) menstrual cycle. Applying World Health Organization criteria (12, 13), the resulting degrees of hyperglycemia were classified as DM, IGT, and impaired fasting glucose (IFG). Blood samples were drawn in the morning, between 8 and 10 AM, after an overnight fast. At the same time, the age, blood pressure, body weight, body height, and waist and hip circumferences of each patient were measured and recorded (12, 14–16).

Patients underwent IVF (insulin sensitizer was discontinued before the start of leuprolide acetate injection) and were encouraged to do more exercise and change their lifestyle to obtain better results (18–20).

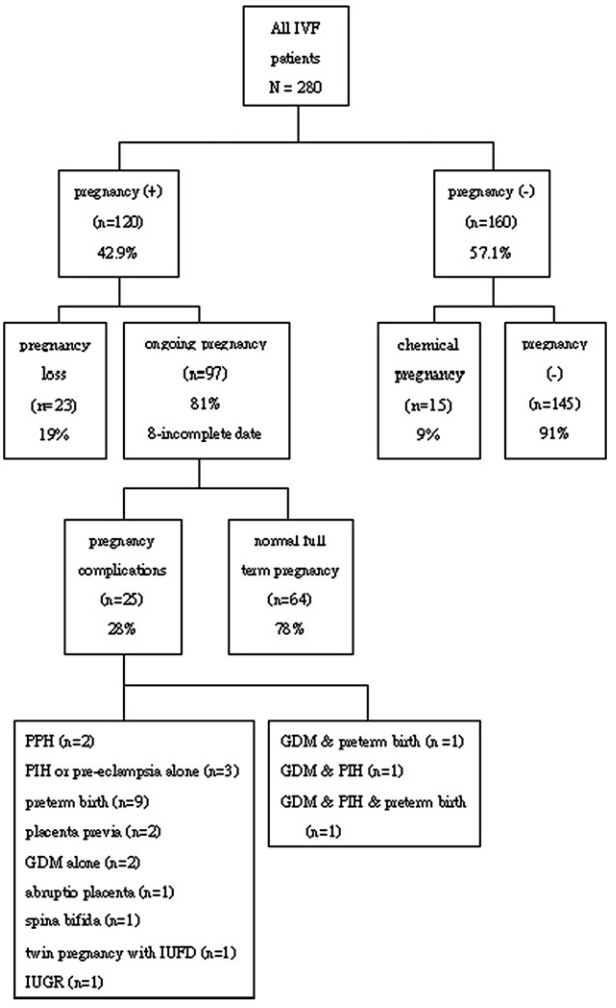
Pregnancy testing was performed 10 days after embryo transfer. An hCG level of <10 mIU/mL on the first determination was defined as nonpregnancy. If the hCG was >10 mIU/mL, the titer was repeated every 2 days. A biochemical pregnancy was diagnosed when the hCG level decreased before the gestational sac was visualized by transvaginal ultrasonography. Pregnancy loss was defined by an arrest of growth of the gestational sac, ectopic pregnancy, or loss of pregnancy before 20 weeks of gestational age.

Patients who delivered before 37 weeks were designated as having a preterm birth (1, 16). Patients who had a 2-hour serum glucose level of >140 mg/dL after a 50-g oral glucose load at 24–28 weeks of gestation were considered to have an abnormal glucose screening result and were further evaluated by using a diagnostic 100-g oral glucose test. According to the National Diabetes Data Group criteria, GDM was diagnosed if two or more glucose values were abnormal (i.e., >105, 190, 165, and 145 mg/dL at fasting and at 1, 2, and 3 h after glucose administration, respectively) (13, 15).

Pregnancy-induced hypertension was defined as a maternal diastolic blood pressure of ≥90 mm Hg during pregnancy, on two consecutive readings taken 4 hours apart, or on a single reading of ≥110 mm Hg. Pre-eclampsia was defined as hypertension with the presence of significant proteinuria after 20 weeks of pregnancy (16, 17).

FIGURE 1

Flow chart of patient outcomes. PIH = pregnancy-induced hypertension; PPH = primary pulmonary hypertension; IUFD = intrauterine fetal death; IUGR = intrauterine growth restriction.



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In Vitro Fertilization Cycle Protocol

Premedication with triphasic oral contraceptive pills was started on the 5th day of the menstrual cycle, 1 month before the IVF stimulation protocol commenced. Leuprolide acetate (Lupron; Takeda Pharma, Osaaka, Japan) was started on the 21st day of the cycle and continued for 12–17 days at a dosage of 0.5 to 1 mg/d.Gonal-F (Serono Pharma, Bari, Italy; 225–375 mg) was used to induce ovulation, and the dosage was decreased depending on the patient response. When there were more than two to three dominant follicles of >17 mm in diameter, hCG (10,000 IU, Serono Pharma) was injected, and ultrasound-guided transvaginal oocyte retrieval was performed 32–36 hours later, followed by insemination or intracytoplasmic sperm injection on the same day. After culture in human tubal fluid (Irving Scientific, Santa Ana, CA) with

10%–15% of maternal serum for 3 days, up to four embryos were transferred to the patient.

Assay

Plasma glucose levels were determined by the glucose oxidase technique and were analyzed 30 minutes after the blood was drawn. Serum insulin samples were stored at –20°C, androstenedione samples were stored at –80° C, and both were analyzed by RIA within 7 days of sampling (Diagnostic Products Corporation, Los Angeles, CA). Samples were analyzed for FSH, LH, T, PRL, and E_2 levels by RIA (Diagnostic System Inc., Webster, TX) on the same day that blood extraction was performed. The intra-assay and interassay coefficients of variation were 3.5% and 5.6% for glucose, 2.5% and 7.1% for FSH, 6.5% and 7.4% for LH, 7.5% and 8.5% for T, 3.7% and 5.4% for androstenedione, 2.6% and 5.4% for PRL, 1.65% and 2.87% for E_2, and 8.7% and 9.4% for insulin, respectively.

Statistical Analysis

Analysis of variance and Student's *t* tests were used to determine statistical significance. Logical linear regression was used to compare the correlation between insulin resistance and birth weight of singleton full-term newborns. The general linear model (21, 22) was used to perform both age and BMI covariance adjustments. Receiver operating characteristic (ROC) curves were used to compare insulin resistance between preterm birth and normal, full-term birth patients. Youden's J index was used to select the cutoff from the ROC curve results (23–25).

Data analysis was performed by using the Statistical Package for the Social Sciences (version 11.0; SPSS Inc., Chicago, IL) and Excel (Microsoft Corporation, Redmond, WA). A value of $P<.05$ was considered statistically significant.

RESULTS

One hundred twenty of 280 first–IVF cycle patients achieved pregnancy, for a pregnancy rate of 42.9% (Fig. 1). There were 23 (19%) pregnancy losses. There were no statistical differences in age, BMI, waist-to-hip ratio, FSH, LH, T, fasting glucose and insulin, 2-hour glucose, and 2-hour insulin levels, and the homeostatic model assessment of insulin resistance (HOMA IR) between the pregnancy and non-pregnancy groups or between the pregnancy loss and ongoing pregnancy groups.

In 8 of the 97 patients with ongoing pregnancy, only the birth weights of the newborns were recorded. Because information was lacking regarding their prenatal follow-up, these women therefore were excluded from further analysis. In the remaining 89 patients, 25 patients had various complications of pregnancy, whereas 64 patients had normal full-term pregnancies.

The pregnancy group with complications was significantly older, weighed more, and had higher fasting glucose levels than did the normal, full-term pregnancy group ($P=.018$ for age; $P=.022$ for BMI; $P=.020$ for fasting glucose); however, after adjustment for age and BMI (21–23), fasting glucose levels were not statistically different (Table 1). For the non-pregnancy group, 15 patients had biochemical pregnancies, and 145 patients had a negative hCG. In the biochemical group with pregnancy losses, the LH and 2-hour insulin levels were statistically significantly higher than those in the patients with a negative hCG (Wei J-W, Young R, Kuo I-L, Liaw C-M, Chiang H-S, Yeh C-Y, unpublished data; $P=.05$ for LH and $P=.009$ for 2-h insulin).

Among the 25 patients who had pregnancy complications, there was 1 patient who had both GDM and a preterm delivery; 1 patient who had both GDM and pregnancy-induced hypertension; and 1 other patient who had GDM, pregnancy-induced hypertension, and a preterm birth. When we compared the 11 preterm patients with the 64 full-term pregnancy patients, the preterm group had statistically significantly higher BMI, levels of fasting glucose and insulin and of 2-hour glucose, and HOMA IR.

There was no difference between the 40 patients with singleton births (62.5%) and those who had full-term multiple births, except for a higher BMI in the singleton-pregnancy group. The ROC curves (Fig. 2) for BMI; levels of fasting glucose, fasting insulin, and 2-hour glucose; and HOMA IR between preterm and full-term births (23–25) showed that the fasting glucose level of preterm birth patients was more likely to be >98.5 mg/dL, with a sensitivity of 73% and a specificity of 73%, and the 2-hour glucose level was more likely to be >101.5 mg/dL, with a specificity of 72.4% and a sensitivity of 54%. The area under the ROC curve was 0.759 (95% confidence interval, 0.62–0.898) for fasting glucose and was 0.655 (95% confidence interval, 0.463–0.847) for 2-hour glucose levels.

In the 11 patients with preterm births, there was 1 patient with IGT, 1 patient with IFG, and 1 patient with DM who were first diagnosed by preconception OGTT screening and World Health Organization criteria (IFG: fasting glucose, ≥110 mg/dL; IGT: 2-h glucose, ≥140 mg/dL; and DM: 2-h glucose, ≥200 mg/dL). Of the five patients who delivered after 30 weeks of gestation, two had GDM. The remaining six patients delivered between 20 and 26 weeks of gestation; none of the six patients had undergone gestational glycemic screening tests, as recommended by the National Diabetes Data Group (13, 16) before their preterm delivery. Most preterm birth patients had a greater BMI compared with normal, full-term patients ($P=.017$), but there was one exception, a patient who had IFG and a BMI of only 19.8.

We also compared all the parameters between the singleton and multiple pregnancies. Except for a higher BMI (Wei J-W, Young R, Kuo I-L, Liaw C-M, Chiang H-S, Yeh C-Y, unpublished data; $P=.04$) in the singleton group, there was no statistical difference between the two groups. Our data showed that patients with preterm births, but not patients with multiple pregnancies, had higher fasting and 2-hour glucose levels and that patients with multiple pregnancies tended to have lower BMI before their pregnancy.

TABLE 1

Comparison between the different pregnancy outcome groups.

Parameter	Pregnancy with complications (A) (n = 25)	Preterm (B) (n = 11)	Full-term pregnancy (C) (n = 64)	*P* values: A and C comparison	*P* values: B and C comparison
Age (y)	37.08 ± 7.34	37.36 ± 10.63	34.20 ± 3.83	.018	.072
BMI (kg/m^2)	22.68 ± 4.41	23.46 ± 5.91	20.97 ± 2.36	.022	.017
Waist-to-hip ratio	0.75 ± 0.03	0.75 ± 0.04	0.79 ± 0.30	.592	.730
FSH (mIU/mL)	12.17 ± 2.97	12.52 ± 2.29	13.50 ± 9.32	.504	.743
LH (mIU/mL)	5.41 ± 3.40	5.8790 ± 3.18	7.17 ± 7.92	.306	.613
T (ng/dL)	0.41 ± 0.23	0.53 ± 0.14	0.33 ± 0.23	.170	.003
A (ng/mL)	1.63 ± 0.68	2.01 ± 0.71	1.68 ± 0.69	.757	.196
Fasting glucose (mg/dL)	100.76 ± 15.27	107.36 ± 20.60	95.14 ± 7.18	.020	< .001
2-h Glucose (mg/dL)	109.64 ± 33.43	120.55 ± 46.99	99.97 ± 19.71	.095	.015
Fasting insulin (μIU/mL)	7.16 ± 10.07	10.55 ± 14.33	6.20 ± 3.75	.513	.039
2-h Insulin (μIU/mL)	29.91 ± 17.73	31.60 ± 23.86	29.00 ± 23.31	.865	.745
HOMA IR	2.09 ± 3.85	3.43 ± 5.58	1.45 ± 0.93	.216	.009

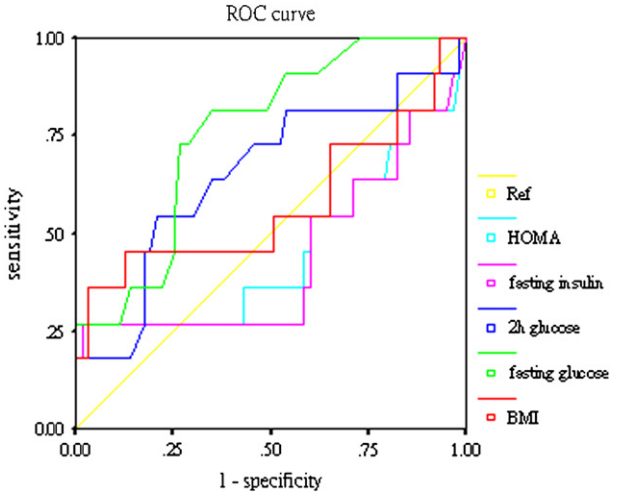
Note: Data are mean ± SD unless otherwise indicated.

Wei. Abnormal OGTT and IVF pregnancy outcome. Fertil Steril 2008.

Linear regression comparing the birth weight of full-term singletons and preconception glycemic parameters (Fig. 3) showed that birth weight correlated positively with fasting insulin (P=.02; R^2 = 0.118), 2-hour glucose (P=.06; R^2 = 0.0851), and 2-hour insulin (P=.08; R^2 = 0.0834) levels and with HOMA IR (P=.02; R^2 = 0.1297).

FIGURE 2

Receiver operating characteristic curves for BMI; levels of fasting glucose, fasting insulin, and 2-hour glucose; and HOMA IR, comparing preterm and full-term births.



Wei. Abnormal OGTT and IVF pregnancy outcome. Fertil Steril 2008.

DISCUSSION

We found no association between OGTT parameters and IVF pregnancy results, nor could pregnancy loss be predicted. Patients with pregnancy complications weighed more, were older, and had higher fasting glucose levels than did normal, full-term patients but failed to show any significant difference after adjustment for age and BMI. It appears that the factor of advanced maternal age was associated with a higher BMI and more pregnancy complications.

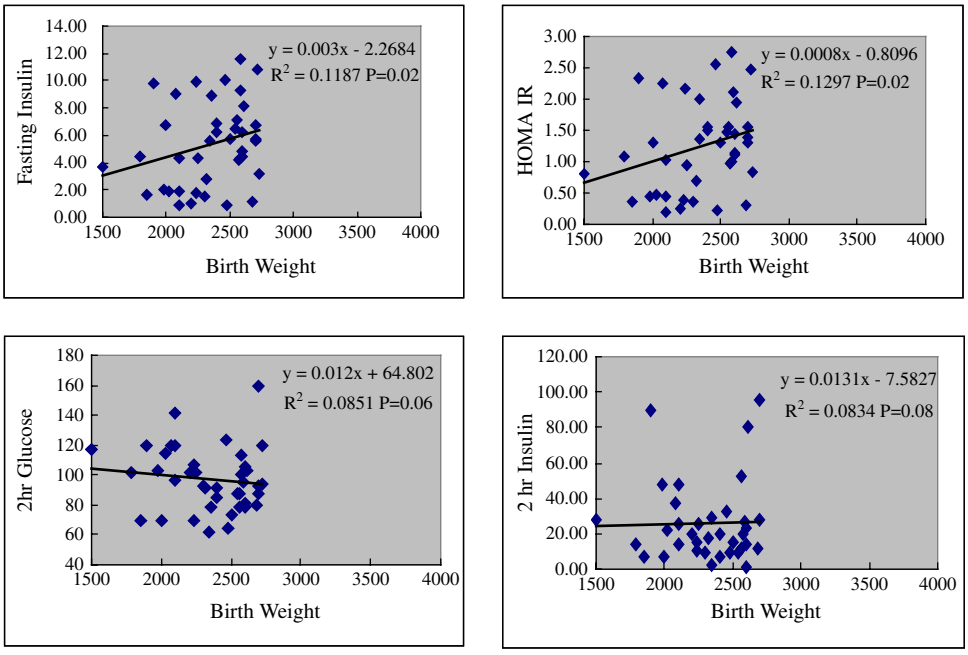
Insulin resistance was not associated with all of the pregnancy complications (26, 27) that were observed in our patients. However, patients with preterm births had higher BMI, fasting glucose, fasting insulin, and 2-hour glucose levels and had a higher HOMA IR than did the normal, full-term patients. Receiver operating characteristic curve analysis showed a fasting glucose of >98.5 mg/dL and a 2-hour glucose of >101.5 mg/dL, which may serve as criteria for the increased risk of preterm birth.

Linear regression demonstrated that the birth weight of normal, full-term pregnancies was positively related to fasting insulin, 2-hour glucose, and 2-hour insulin levels and to HOMA IR. All patients were encouraged to follow a healthy lifestyle before their scheduled IVF cycle. Perhaps it was because of this that although the birth weight of singleton pregnancies showed some association with 2-hour glucose and 2-hour insulin, those relationships failed to reach statistical significance. However, there was a significant relationship with the birth weight for both HOMA IR and fasting insulin.

It is unclear whether gestational hyperglycemia is associated with an increased risk of preterm birth (4, 14, 15). Some studies have shown no increase in preterm labor and

FIGURE 3

Linear regression between fasting insulin, 2-hour glucose, 2-hour insulin, and HOMA IR and birth weight in singleton, full-term pregnancies.



Wei. Abnormal OGTT and IVF pregnancy outcome. Fertil Steril 2008.

premature rupture of membranes (1–4) with increasing glucose intolerance. But others have supported such a correlation (12, 28, 29).

All these data have been confounded by heterogeneous races among the studies and a lack of preconception OGTT data, and most studies have been retrospective. In contrast, we had a homogenous racial group (i.e., Chinese), we performed a preconception OGTT, and our study was prospective by design. In vitro fertilization offers a quick glimpse into the relationship between OGTT and pregnancy outcome in a relatively short span of time.

In the 11 patients with preterm births, there was one patient with IGT, one patient with IFG, and one patient with DM, all of whom were diagnosed by using a 75-g glucose tolerance test. Most of the patients had a higher BMI compared with the normal, full-term group (P=.017), with the exception of one patient who had a BMI of 19.8. There were six patients who had preterm births between 20 and 26 weeks of gestation, and none of the six patients had undergone the scheduled gestational glycemic screening test as recommended by the NDGG (13,16). It may be that the NDGG-recommended GDM screening and intervention came too late for these patients.

In a retrospective study based on gestational OGTT, Nordin et al. (16) reported that early diagnosis and early intervention can prevent many diabetes-related complications. In our study, we correlated abnormal preconception OGTT results with preterm birth in our IVF patients, and we therefore suggest that the gestational OGTT and GDM intervention should be scheduled earlier for such patients. Our research suggests that a fasting glucose level of >98.5 mg/dL or a 2-hour glucose level of >106.5 mg/dL can identify those who are at high risk for preterm birth. Furthermore, in normal, full-term patients, our OGTT results suggest that birth weight correlated positively with IR. Insulin resistance in our Chinese population, although absolutely lower compared with other studies, still correlated with birth weight (11, 12, 21, 24).

Gestational hyperglycemia has been demonstrated to increase the incidence of pregnancy complications (22–26), with macrosomia being one of the most common pregnancy complications (12, 14). In our study, using the preconception oral glucose tolerance data, there was no difference between the normal, full-term birth and pregnancy-with-complications groups; our study population also did not have any case of macrosomia as a complication. We did not find that glucose levels changed pregnancy outcome.

Some studies have shown that IR increases pregnancy loss rates (1–6, 16, 26, 27); however, in our study, we found no such effect. This may be because we collected only IVF preconception glucose tolerance data. Patients were advised to exercise more and change to a healthier lifestyle to have a better chance of achieving pregnancy (17). This may have obliterated the preconception OGTT advantage and resulted in failure to show association between the study variables and pregnancy loss.

It is well established that upper genital tract infections and/or inflammation are associated with preterm labor and birth (30). Whether gestational hyperglycemia increases the incidence of preterm labor is still controversial. Most studies have focused on maternal–fetal outcomes in GDM, but few have dealt with the effects of glucose intolerance. There are increasing data supporting the increased incidence of macrosomia or pregnancy-induced hypertension with gestational hyperglycemia. But few studies have dealt with the increase in preterm births, and most reports have been correlated with gestational OGTT and were retrospective in nature.

Our study is one of the few to compare data from preconception OGTT with pregnancy outcome in IVF patients. We found that IR did not influence the IVF pregnancy outcome but had an impact on preterm birth. For our patients, who have comparatively smaller BMI (an average of 21.2 kg/m^2) in contrast with Caucasians (23), glucose intolerance is nevertheless present and may play an important role in preterm birth. We recommend administering the OGTT to our infertility patients even if they are physically slim. Early intervention and close follow-up for patients with IR may help to prevent preterm birth (16, 31).

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