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Role of the Glucose Tolerance Test as a Predictor of Preeclampsia

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Key Words
Preeclampsia · Uterine artery Doppler · Oral glucose tolerance · Second-trimester screening

Abstract
Objective: To determine whether oral glucose tolerance tests (OGTT) play a role as predictors of preeclampsia (PET) in pregnant women. ***Methods:*** A retrospective case-control study was conducted in 2,002 singleton pregnancies that had a uterine artery (UtA) Doppler at 22–25 weeks and an OGTT. The UtA Doppler and OGTT were adjusted based on maternal characteristics, and the results were expressed as multiples of the expected normal median and compared between groups. Logistic regression analysis was used to determine whether maternal characteristics, OGTT, and UtA Doppler significantly contribute to the prediction of early- (<34 weeks), intermediate- (34–37 weeks), or late-onset (>37 weeks) PET. The performance of the screening was determined by ROC curves. ***Results:*** Women who developed PET were characterized by an older maternal age, an increased body mass index, and an altered UtA Doppler. The group with intermediate-onset PET was the only one associated with higher 2-hour OGTT levels compared to controls. Combined models were developed via logistic regression analysis using maternal characteristics, UtA Doppler, and OGTT to predict PET. These combined models were able to detect around 74, 42, and 21% of women who later developed early-, intermediate-, or late-onset PET, respectively, with only a 5% false-positive rate. ***Conclusions:*** This study shows that the combination of maternal characteristics, second-trimester UtA Doppler, and OGTT is a predictor of the development of PET in healthy pregnant women.

Introduction

Preeclampsia (PET) is a multisystemic disorder of unknown cause that is characterized by abnormal spiral artery remodeling [1] which is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system, and endothelial cell dysfunction [2]. One of the theories on the pathophysiology of PET was described by Redman and Sargent [3], who proposed that all pregnancies are characterized by a grade of endothelial dysfunction/activation which leads to a systemic inflammatory response due to shedding of apoptotic debris into the maternal circulation [3], with PET being therefore just an exaggerated response to this physiological event which can be triggered by larger or oxidatively stressed placentae [3].

Normal pregnancy is also characterized by a degree of insulin resistance, hyperlipidemia, and an increase in co-

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agulation factors to meet the metabolic demands of the growing fetus [4]. On the other hand, pregnancy-induced hypertension has also been associated with the insulin resistance syndrome (also called the metabolic syndrome) which includes hypertension, hyperinsulinemia, glucose intolerance, obesity (particularly central), and lipid abnormalities (including elevated triglyceride levels) [5]. Other accompanying alterations may include elevated levels of leptin, TNF-α, tissue plasminogen activator, plasminogen activator inhibitor-1, and testosterone [5].

The features of PET (hypertension, endothelial cell dysfunction, and lipid alterations) are also features of the insulin resistance syndrome [6], and thus insulin resistance may play a role in the development of preeclamptic syndrome [4].

The gold standard for the diagnosis of insulin resistance is the hyperinsulinemic euglycemic clamp. However, this is considered impractical for routine clinical use; therefore, a minimal model assessment [dynamic testing with oral glucose loading – oral glucose tolerance test (OGTT)] and homeostatic models (glucose and insulin measurements obtained from fasting states – HOMA, QUICKI) have been used for this purpose [7, 8]. Kirwan et al. [9] validated the homeostatic models for use in pregnancy, although the OGTT is also used in pregnancy for the diagnosis of gestational diabetes [10].

The aim of this study was to determine whether glucose tolerance testing can play a role as a predictor of PET in healthy pregnant women.

Patients and Methods

Participants and Study Design

This was a retrospective cohort study conducted on 2,002 singleton pregnancies that had a uterine artery (UtA) Doppler at 20^{+0}–24^{+6} weeks of gestation, an OGTT, and delivery at our hospital during 2004–2010. In selecting the subject and control groups for this study, we excluded 37 women who had gestational diabetes mellitus with fasting and/or 2-hour glucose levels greater than 105 or 200 mg/dl, respectively, 98 women with small-for-gestational-age infants, and 93 women with maternal chronic disease, gestational hypertension, placental abruption, or major fetal abnormalities, leaving 84 women who later developed PET and 1,690 unaffected women. Pregnancies that developed PET were subclassified based on the gestational age at delivery as: early-onset if the delivery was before 34^{+0} weeks, intermediate-onset if it was between 34^{+0} and 36^{+6} weeks, or late-onset if the delivery was after 37^{+0} weeks.

A UtA Doppler was performed by obstetricians at our Fetal Medicine Unit who were supervised by one of the authors (M.P.-C.) accredited by The Fetal Medicine Foundation of London (www.fetalmedicine.com). A transvaginal UtA color Doppler was carried out using an Aloka® 3500 or 4000 scanner with a 5- to 7.5-MHz transducer. The mean pulsatility index (PI) was calculated based on 3 consecutive waveform readings.

All patients in this study also had the World Health Organization (WHO) 75-gram OGTT between 24 and 28 weeks of gestation. Patients were considered to have gestational diabetes if the result was higher than 105 mg/dl for fasting glucose levels or higher than 140 mg/dl after 2 h (2-hour glucose). We also recorded the maternal age, smoking status, parity, body mass index (BMI) at booking, and maternal and perinatal outcomes.

Unaffected pregnancy, considered the control group, was defined as a pregnancy in which the mother had a normal blood pressure (≤140/90 mm Hg), absent proteinuria, and no medical complications. PET was defined as a maternal blood pressure ≥140/90 mm Hg with proteinuria (300 mg/24 h) and resolution of hypertension and proteinuria following delivery.

Statistical Analyses

The Kolmogorov-Smirnov test was used to assess the normality of continuous data. Firstly, as previously described by the Fetal Medicine Foundation group [11], glucose values and UtA Doppler mean PI values were log transformed, adjusted based on clinical characteristics, and converted to multiples of the expected normal median (MoM) of the unaffected group. Secondly, a logistic regression analysis was used to determine whether significant maternal characteristics, UtA Doppler MoM values, and OGTT MoM values significantly contribute to the prediction of early-, intermediate-, or late-onset PET. Finally, the performance of the screening was determined by receiver operating characteristic (ROC) curves.

Comparisons between groups were performed using the Kruskal-Wallis test and in cases of significant differences the Mann-Whitney U test was performed between PET groups and controls. Categorical variables were compared using a χ^2 test. $p < 0.05$ was considered statistically significant.

Results

The maternal and perinatal characteristics of the different groups are shown in table 1. Pregnant women who subsequently developed PET were older [mean age 32.0 years (IQR 27.1–36.9) vs. 29.9 years (IQR 25.0–34.0), $p < 0.05$] and had a higher BMI [mean 26.7 (IQR 23.6–30.7) vs. 24.5 (IQR 22.2–27.3), $p < 0.05$] than women in the control group, especially those who delivered with intermediate- and late-onset PET (table 1). Furthermore, they had an increased chance of cesarean section (71.4 vs. 45.0%, $p < 0.05$) and an increased preterm delivery rate (45.2 vs. 7.6%, $p < 0.001$) compared to the control group. Although there were no significant differences in nulliparity rates between women with PET and the control group (48.8 vs. 41.8%), this characteristic was significantly different in patients who subsequently developed early-onset PET (table 1). Women who later developed PET were associated with double the rate of gestational diabe-

Table 1. Demographic characteristics of the study groups

	Control (n = 1,690)	Early PET (n = 19)	Intermediate PET (n = 19)	Late PET (n = 46)
Maternal age, years	29.9 (25.0–34.0)	31.8 (26.7–38.2)	33.6 (29.2–38.1)[a]	31.4 (25.9–36.2)
BMI	24.5 (22.2–27.3)	24.9 (23.3–27.2)	25.8 (23.5–32.9)[a]	28.6 (24.1–32.0)[a, b]
Smoking	140 (8.3)	2 (10.5)	2 (10.5)	2 (4.3)
Nulliparity	706 (41.8)	14 (73.7)[a]	10 (52.6)[b]	17 (37.0)[b, c]
Cesarean rate	761 (45.0)	19 (100.0)[a]	15 (78.9)[a]	26 (56.5)[b, c]
GA at delivery, weeks	39.0 (38.2–39.6)	30.0 (28.3–32.6)[a]	35.3 (34.4–36.3)[a, b]	38.1 (37.6–39.0)[a–c]
Birth weight, kg	3.45 (2.92–3.76)	1.26 (0.94–1.71)[a]	2.28 (2.00–2.86)[a, b]	3.10 (2.84–3.68)[a–c]
Birth weight percentile	57.3 (37.8–78.1)	21.3 (7.3–60.6)[a]	27.4 (7.4–48.3)[a]	38.9 (19.9–75.1)[a–c]
Fetal growth restriction	0 (0.0)	7 (36.8)[a]	8 (42.1)[a]	6 (13.0)[a–c]
Gestational diabetes	159 (9.4)	4 (21.1)[a]	6 (31.6)[a]	4 (8.7)[b, c]

Results are expressed as medians (IQR) or n (%) unless otherwise indicated. GA = Gestational age. [a] vs. controls. [b] vs. early PET. [c] vs. intermediate PET.

Table 2. UtA Doppler and maternal OGTT results in women who developed PET and controls

	Control (n = 1,690)	Early PET (n = 19)	Intermediate PET (n = 19)	Late PET (n = 46)
MoM fasting glucose, mg/dl	0.99 (0.94–1.16)	0.95 (0.91–1.04)	1.00 (0.94–1.13)	0.99 (0.93–1.11)
MoM 2-hour glucose, mg/dl	1.00 (0.87–1.14)	1.00 (0.87–1.18)	1.06 (0.94–1.36)[a]	1.06 (0.91–1.17)
MoM mean PI UtA Doppler	0.98 (0.84–1.16)	1.96 (1.32–2.22)[a]	1.57 (1.05–1.84)[a]	1.30 (0.96–1.54)[a]

Results are expressed as medians (IQR). [a] $p < 0.05$ compared to the control group.

tes compared to the control group (16.7 vs. 9.4%, $p < 0.05$), and this was more frequently seen in early and intermediate PET (table 1). Finally, as expected, we observed a significant difference between PET groups with regard to gestational age at delivery and birth weight percentile as an expression of severity (table 1).

Multiple regression analysis of the unaffected group demonstrated that significant independent contributions to the log fasting glucose and 2-hour glucose were made by maternal age, BMI, and parity, although none of the maternal characteristics analyzed affected the log UtA Doppler mean PI.

There was a significant increase in the UtA Doppler mean PI MoM between each of the PET groups and the control group (table 2; fig. 1b). However, the 2-hour glucose MoM was increased only in the intermediate-onset PET group compared to controls (table 2; fig. 1a). There was no significant difference between groups in fasting glucose levels (table 2).

Logistic regression analysis using a backward conditional test demonstrated that the following independent variables were significant predictors of the development of early-, intermediate-, and late-onset PET: early-onset PET = –12.656 + 0.131(maternal age) + 2.085(nulliparity) + 2.346(UtA Doppler MoM); intermediate-onset PET = –10.952 + 0.091(maternal age) + 1.182(UtA Doppler MoM) + 2.086(2-hour glucose MoM), and late-onset PET = –6.088 + 0.024(BMI) + 1.590(UtA Doppler MoM).

We also performed an ROC curve analysis comparing the performance of different models to detect PET (table 3; fig. 2). Maternal characteristics alone can detect about a third of early-onset cases with a 5% false-positive rate, but just 1 in 10 women who subsequently develop late-onset PET are detected. After including UtA Doppler in the model, the detection rate for early- and late-onset PET increased to 74 and 21%, respectively. Moreover, the model for intermediate-onset PET, which includes 2-hour glucose and UtA Doppler, can detect about 43% of cases. If the 2-hour glucose test is excluded from the above mentioned model, the detection rate for a 5% false-positive rate reaches the same value, but the area under the ROC curve is lower than for the model that includes UtA Doppler [0.76 (0.64–0.88) vs. 0.79 (0.67–0.90)].

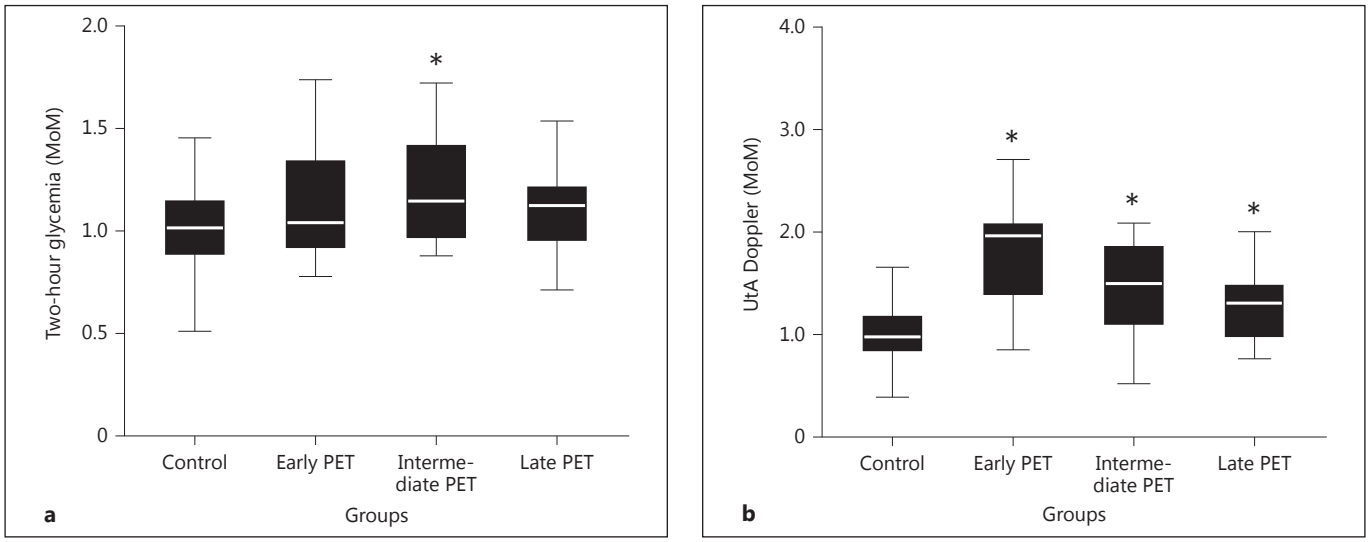

Fig. 1. Two-hour glucose levels (**a**) and UtA Doppler mean PI (**b**) expressed as MoM of the unaffected group in women in the early-, intermediate-, and late-onset PET groups and in the control group. * PET groups vs. the control group ($p < 0.05$).

Table 3. Comparison of performances in the prediction of pre-eclampsia based on maternal history and a combined model

Models	Detection rate with a 5% FPR, %		
	early PET	intermediate PET	late PET
History alone	26.3	15.8	11.9
Combined model	73.7	42.1	21.4

History alone: maternal age and parity for early and intermediate PET and BMI for late PET. Combined model: history + (UtAD for early PET; UtAD and 2-hour glucose levels for intermediate PET, and BMI for late PET). FPR = False-positive rate.

Discussion

This study shows that although the 2-hour glucose during the second trimester of pregnancy was significantly increased in women who subsequently developed PET between 35 and 37 weeks of gestation, the main predictors of all kinds of PET were maternal clinical characteristics and the UtA Doppler mean PI.

Women who were destined to develop PET, especially intermediate- and late-onset PET, were older and had a higher BMI than women in the control group, in agreement with previous studies [12, 13]. Sibai et al. [2] described that obesity has a strong link with insulin resistance, which is also a risk factor for PET. The exact mechanism by which obesity or insulin resistance is associated with the disorder is not completely understood. Possible explanations are increased shear stress associated with hyperdynamic circulation, dyslipidemia or enhanced cytokine-mediated oxidative stress, amplified sympathetic activity and increased tubular sodium resorption, and direct interference of insulin resistance and therefore a hyperinsulinemic state with physiogical placentation [12].

In the current study, as we have described previously [14], the UtA Doppler mean PI was significantly higher in all PET groups than in the unaffected group, and it increased the possibility of developing early-onset PET by around 15-fold. As we know, UtA Doppler has been assessed as a useful screening test for the prediction of pregnancies at risk for complications of impaired placentation, including PET and fetal growth restriction [15]. Pregnancies with abnormal UtA Doppler findings during the second trimester are associated with a more than 6-fold increase in the rate of PET [16]. However, screening tests by UtA Doppler at 23 weeks of gestation can only predict 40% of all PET cases with a 5% false-positive rate, though this test is able to detect around 80% of women who later develop severe cases [17].

Interestingly, the other predictor in our study of PET was the adjusted 2-hour glucose MoM level. The intermediate-onset PET group showed a slightly higher 2-hour glucose MoM compared to the control group. There is dis-

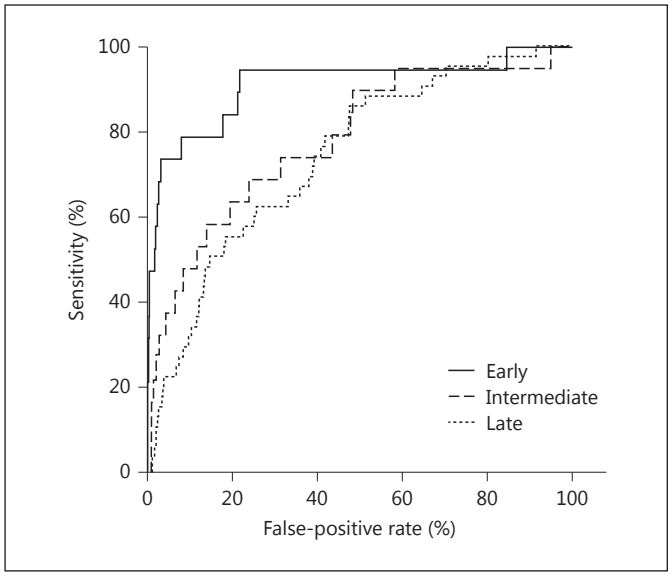

Fig. 2. ROC curves for the prediction of early-, intermediate-, and late-onset PET by different models.

crepancy in the literature about the relationship between insulin resistance and PET. In established PET, some groups have shown that there is an exaggerated hyperinsulinemia (elevated fasting insulin levels after an OGTT) [18–20]; by contrast, it has also been described that PET is associated with increased insulin sensitivity [21] or has no relationship with insulin resistance measured by the euglycemic clamp technique or minimal model analysis [21, 22]. These discrepancies in the literature about the relationship between insulin resistance and PET might be explained by inadequate study designs (small sample sizes), the application of unsatisfactory techniques for assessing insulin resistance, and/or as secondary to an inadequate classification of this disease which is considered nowadays to be a complex syndrome associated with an exaggerated inflammatory response [23].

In agreement with our data, there are some publications showing that higher plasma glucose levels (after glucose loading) and lower sex hormone-binding globulin (negatively correlated with insulin resistance) were present in women who subsequently developed PET [24, 25]. Furthermore, the original HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study demonstrated that there was a significant association between fasting and 2-hour glucose levels and the risk of developing PET in women who had an OGTT between 24 and 32 weeks of gestation [26]. A subanalysis of the HAPO study [27] including 1,116 PET pregnancies and 20,248 normotensive pregnancies corroborated the previous finding that the risk of developing PET rises with increasing OGTT plasma glucose (fasting and 2-hour glucose), though this risk after adjustment for insulin resistance (C-peptide) was weaker. Moreover, there are two publications dealing with the role of second-trimester insulin resistance in predicting PET. The first study, including 2,954 singleton pregnancies delivered at term, concluded that both C-peptide-to-glucose ratios at fasting and at 2 h after loading, as markers of insulin resistance, were significantly higher in women who later developed gestational hypertension compared to the control group. This finding was not related to PET [28]. On the other hand, Hauth et al. [29], in a study of the role of second-trimester insulin resistance (fasting glucose and HOMA-IR) as a predictor of PET, concluded that the detection rate for this disease was about 40% with a 25% false-positive rate.

The finding of this study that there were increased 2-hour glucose levels and BMI in women who were destined to develop intermediate- or late-onset PET are consistent with the hypothesis that insulin resistance might be part of the pathophysiology of this syndrome [23]. It has also been reported that first-trimester adiponectin, an adipocyte-derived factor which correlates with systemic insulin sensitivity [3, 5, 30, 31], is lower in women who subsequently develop PET than in controls [21, 32]. Furthermore, D'Anna et al. [33] confirmed that a PET group (particularly late-onset cases) had significantly lower first-trimester plasma levels of adiponectin and higher HOMA values than the control group, suggesting that insulin resistance could help predict two different subgroups of PET [33]. The explanation for this result is also in agreement with a new hypothesis about the genesis of this disease, which considers the condition to be a syndrome where the second stage of the disease is triggered by poor placentation and/or proinflammatory factors associated with insulin resistance and hyperlipidemia [23, 34].

In conclusion, our results support the hypothesis that insulin resistance plays a role in the pathogenesis of PET and demonstrate that 2-hour glucose levels, in addition to maternal characteristics and UtA Doppler, might help predict the development of PET, especially in women who deliver after 34 weeks. Considering these results, firstly, a future predictive first-trimester study is required to prove whether insulin resistance markers, including direct and indirect ones, are really associated with any form of PET, and especially with late-onset cases. Secondly, after proving this association, it would be possible to organize randomized trials to evaluate the potential for treatment with insulin sensitizers to prevent PET.

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