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The threshold criteria for the 75g oral glucose tolerance test in pregnancy and short-term adverse pregnancy outcomes

C. Savona-Ventura, M. Chircop

Diabetic Pregnancy Joint Clinic, Department of Obstetrics-Gynaecology, St. Luke's Teaching Hospital, Malta

Abstract
The significant threshold values for the 75g oGTT during pregnancy have yet to be conclusively determined. The study aims to identify the risk significance of a borderline oGTT result. Women undergoing a 75g OGTT during the third trimester of pregnancy were classified into two groups - borderline tolerance (2-h post-load glucose 8.0-8.5 mmol/l: n=75), and GDM (≥8.6 mmol/l: n=236). Outcome indicators of these two groups of women were compared to the parameters of the women with a presumed normal carbohydrate metabolism (n = 12185). GDM women showed themselves to be at a significantly increased risk of developing hypertensive disorders during pregnancy and to require obstetric intervention in the form of induction of labour and caesarean section. Their infants were more likely to be macrosomic or preterm and having a low Apgar score at birth. Shoulder dystocia was similarly more likely in infants born to GDM mothers. Women with borderline glucose tolerance did not in any way show any statistically significant increased predisposition to these complications. It would appear the significant threshold for the 75g oGTT during pregnancy should be of the order proposed by the American Diabetes Association criteria where the 2-hour post-load glucose value is ≥ 8.6 mmol/l.

Key words: *Diabetes mellitus, pregnancy, diagnosis, complications*

Introduction

The current classification and diagnostic criteria for diabetes mellitus were endorsed by the World Health Organisation in 1980, with modifications in 1985 and 1994.[1] Controversy however still exists as to what test is suitable for the diagnosis of gestational diabetes, though the endorsement of the 75g load by the Fourth International Workshop on Gestational Diabetes Mellitus [GDM] in 1997 should have helped break a major stalemate.[2] Interpretation of the 75g oral glucose tolerance test during pregnancy remains a contentious issue since the non-pregnant criteria ignore the "diabetogenic" physiological changes of pregnancy. The current American Diabetes Association criteria for GDM require two plasma glucose values ≥ 5.3 mmol/l (fasting) ≥ 10.0 mmol/l (1 hour) and ≥ 8.6 mmol/l (2 hours).[3] The 1994 WHO criteria for gestational diabetes still required a plasma glucose ≥ 7.0 mmol/l (fasting) or ≥ 7.8 mmol/l (2 hours).[1] The latter diagnostic criteria ignores the physiological changes of pregnancy and thus will include a significant proportion of pregnant women whose carbohydrate metabolism is normal for their pregnant state. The threshold blood glucose levels for the development of complications associated with GDM have yet to be determined. The present study was set up to investigate the risk significance of borderline levels of the 2-hour blood glucose value after a 75-g oGTT performed in the third trimester of pregnancy in a population known to have a high prevalence of carbohydrate metabolism problems, which is reflected in the pregnant population.[4]

Correspondence to: Dr. C. Savona-Ventura, "NorthWynds" 7 Antonio Zammit Street, Gharghur Nxr08, Malta, e-mail: charles.savona-ventura@um.edu.mt

Material & methods

The study reviewed the medical data records of all women delivering in the Maltese Islands during 1999-2001 [n = 12540 maternities resulting in 12714 births]. The medical records revealed a total of 236 women diagnosed as suffering from GDM defined as a 2-h post-75g load glucose value of >8.6 mmol/l and 75 women suffering from borderline glucose tolerance [borderline GT] defined as a 2-h post-load glucose value of 8.0-8.5 mmol/l. The latter group would be considered as suffering from G-IGT by WHO criteria.[1] There were in addition 44 women who suffered from a pre-existing form of diabetes mellitus [pre-DM]. Information pertaining to the national incidence of congenital malformations was made available from the Malta Congenital Anomalies Register for years 1999-2000 [total infants born = 8759, inclusive 212 infants of women with pre-DM and GDM]. During the two-year period no cases of congenital malformations were registered in infants of women with pre-DM while two cases respectively occurred in infants of GDM women. During 2001, a further two cases were registered in GDM women and three cases in pre-DM women.

The outcome parameters of the women with GDM and with borderline GT were compared to the parameters of women with presumed or confirmed normal carbohydrate metabolism [n = 12185]. Glucose tolerance testing is not routinely carried out on all maternities but only in those

women who are considered at particular risk of GDM.[5] During the study period, 6.7% of women [n = 837] were thus assessed during the third trimester of pregnancy. Comparing the incidence rates from this study to previously published prevalence studies,[4] it is estimated that about 31.9% of GDM women are thus identified, while only about 17.7% of women with a borderline GT are identified. The group of patients presumed to have normal carbohydrate tolerance thus includes a small proportion of patients with mild degrees of GDM (estimate ~4%: n = ~487) and borderline GT (estimate ~2.8%: n = ~244). Statistical significance was tested using the Chi Square test analysis using MedCalc (ver.4.16) statistical package. A probability value of <0.05 was taken to represent a significant correlation.

Results

Women diagnosed as suffering from GDM were more likely to have obstetric complications than women with a borderline GT and the total population. These complications serve to increase the mortality and morbidity of both the mother and child [Table 1]. Women with GDM show a statistically significant ($p<0.0001$) increased risk of developing hypertensive disease during the pregnancy when compared to the normal metabolism population. Women with a borderline GT during pregnancy show only a slightly increased risk, which did not show statistical significance ($p = 0.24$). The incidence of multiple pregnancies in GDM appeared to be increased but the difference did not show statistical significance ($p = 0.18$). The women with borderline GT did not show any difference in the multiple pregnancy rate ($p = 0.63$). The pregnancy in the woman with GDM was more likely to terminate in an induction of labour ($p<0.0001$) and caesarean section ($p<0.0001$). The women with a borderline GT did not show any particularly statistically significant increased predisposition to induction or caesarean section rate.

Infants of women with GDM showed a statistically increased risk of a preterm birth ($p = 0.003$); of macrosomia ($p<0.0001$); of shoulder dystocia ($p<0.0001$); and of having a low Apgar score 5 minutes after birth ($p = 0.03$). No such adverse neonatal outcome was noted in infants born to women with a borderline glucose tolerance [Table 2].

Conclusions

In 1980 the World Health Organisation suggested that the criteria used to diagnose diabetes and IGT in the general population could be applied to pregnant women. This view was endorsed in 1985 and 1994.[1] The 1994 WHO criteria for gestational diabetes still required a plasma glucose ≥ 7.0 mmol/l (fasting) or ≥ 7.8 mmol/l (2 hours). These criteria do not take into account the diabetogenic effects of pregnancy. Pregnancy causes postprandial blood glucose values to remain elevated for longer periods of time, hence more mothers are likely to exceed any timed postprandial value and thus be labeled "glucose intolerant" while only displaying the extremes of physiological adaptation. In 1989, the Diabetic Pregnancy Study Group (EASD) in a multicentre European study proposed new higher threshold values for the 75-g glucose tolerance test.[5] These new thresholds required two plasma glucose values of 10.5 mmol/l (1 hour) and ≥ 9.0 mmol/l (2 hours). Similar recommendations were made by the American Diabetes Association that require two plasma glucose values of ≥ 5.3 mmol/l (fasting) ≥ 10.0 mmol/l (1 hour) and ≥ 8.6 mmol/l (2 hours).[3] The latter threshold recommendations appear to be slowly being universally accepted having been adopted by the European Association of Perinatal Medicine.[6]

The significance of the relatively physiologically delayed response to a 75-g glucose load previously considered abnormal by the 1994 WHO diagnostic criteria has still to be determined by large-scale clinical studies, particularly since studies have shown a continuum of risk related to the 2-hour maternal post-75g load blood glucose level for the probability of having an assisted delivery and the likelihood of the baby being admitted to a Special Care Unit, even when the 2-hour value was below 8.0 mmol.[7] Those with a special interest in GDM await the results of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study that should determine clear-cut points for the complications associated with GDM.[8] The present study has confirmed that GDM as defined by the 2-hour value of the ADA criteria is associated by a higher maternal morbidity in the form of an increased risk of hypertensive disease, and more frequent recourse to obstetric intervention. Similarly the infants of GDM mothers showed a higher predisposition to macrosomia, preterm births and low Apgar scores. Women with borderline glucose tolerance as defined by a 2-hour post-75g load glucose value of 8.0-8.5 mmol/l did not exhibit any particular increased risk of maternal or fetal complications.

The study thus endorses the ADA diagnostic criteria as effective threshold levels to relate to clinical risk status. However the outcome indicators assessed in the present study reflect short-term complications only. Minor degrees of glucose intolerance as reflected by borderline glucose tolerance during pregnancy may be attendant by significant long-term outcomes in the mother and child. Maltese women with a borderline glucose tolerance have been shown to be 3.6 times more likely to develop an abnormal glucose tolerance eight years postpartum when compared to women with a normal glucose tolerance test as defined by the WHO criteria.[9] The possible effects of relatively elevated blood glucose levels on the infant's pancreatic development and subsequent adult-onset predisposition to develop IGT/NIDDM still need to be investigated. Gestational Impaired Glucose Tolerance as defined by the 1985 WHO criteria has been shown to be associated with metabolic changes in the infants that reflect a mild derangement to the fetal pancreatic beta cells even though the infant's anthropomorphic characteristics were not adversely altered.[10] In spite of the apparent absence of short-term effects of a borderline glucose tolerance, it may remain prudent to continue advising women with a borderline glucose tolerance test to reduce their refined sugar intake, thus reducing the day-to-day blood glucose loads presented to the developing fetus. The long-term risks to the woman need also be discussed.

Table 1: Maternal Complications

Parameter	Normal metabolism		GDM			Borderline GT		
	No.	%	No.	%	p value	No.	%	p value
❖ Multiple births	159	1.3	6	2.5	0.18	1	1.3	0.63
❖ Maternal PIH/PET	801	6.6	39	16.5	<0.0001	8	10.7	0.24
❖ Induction of labour	4398	36.1	127	53.8	<0.0001	22	29.3	0.28
❖ Caesarean section	2866	23.5	83	35.2	<0.0001	21	28.0	0.44
❖ Operative vaginal delivery	438	3.9	11	4.7	0.49	1	1.3	0.46
Total	12185		236			75		

Table 2: Infant outcome (* based on 1999-2000 data [total infants = 8547])

Parameter	Normal metabolism		GDM			Borderline GT		
	No.	%	No.	%	p value	No.	%	p value
❖ Fetal & neonatal loss	118	1.0	2	0.8	0.91	1	1.3	0.79
❖ Low birth weight [<2.5 kg]	768	6.3	19	7.9	0.38	3	3.9	0.56
❖ Preterm birth [<37 weeks]	759	6.2	27	11.2	0.003	6	7.9	0.70
❖ Infant with RDS	268	2.2	8	3.3	0.34	1	1.3	0.90
❖ Macrosomia [>4.0 kg]	732	6.0	29	12.0	<0.0001	6	7.9	0.65
❖ Shoulder dystocia	51	0.4	10	4.1	<0.0001	0	-	
❖ Apgar ≤ 6 @ 5 min	140	1.1	7	2.9	0.03	1	1.3	0.96
❖ Congenital anomalies	316*	3.7	4	1.7	0.14	2	2.6	0.86
Total	12274		242			76		

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