# The Association of Maternal Antenatal Oral Glucose Tolerance Test and Fetal Congenital Heart Disease

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# The Association of Maternal Antenatal Oral Glucose Tolerance Test and Fetal Congenital Heart Disease

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## ABSTRACT

**Introduction:** Increased risk of congenital heart disease (CHD) has been related with maternal hyperglycemia in gestational diabetes. The aim of this study was to evaluate the association between maternal antenatal oral glucose tolerance test (OGTT) and incidence of fetal CHD. **Method:** This was a retrospective study analyzing maternal antenatal OGTT and antenatally diagnosed CHD of singleton and euploid fetuses in a tertiary maternity hospital. The maternal characteristics and neonatal characteristics were compared among fetuses with and without CHD. The incidence of CHD were compared according to OGTT results. Receiver Operating Curve (ROC) was used to determine the use of maternal antenatal OGTT in predicting the risk of fetal CHD.

**Results:** There were 3,116 women (age 32.3± 4.56 years old) carrying single fetus with normal karyotype who were indicated for OGTT during 5-40 weeks of gestation. The maternal and neonatal characteristics were similar between the CHD and non-CHD groups. The mean values of fasting (4.3 ± 0.2 vs 4.5 ± 0.6; $p$=0.20) and 2-hour post load (6.9 ± 1.5 vs 7.1 ± 1.8; $p$=0.84) glucose level were comparable. Overt diabetes was not observed. Twelve (0.38%) fetuses were diagnosed with CHD. The incidence of CHD were not significantly different between mothers with impaired and normal glucose tolerance. The ROC analysis showed 100% sensitivity when fasting glucose level (FGL) were above 4.0 mmol/l or 2-hours glucose level (2-HGL) more than 4.7 mmol/l.

**Conclusion:** Meaningful OGTT value above which the risk of CHD increased dramatically could not be determined. Neither fasting nor 2-hours post load glucose values of maternal antenatal OGTT appeared to be a predictor of fetal CHD.

**Keywords**: antenatal; congenital heart disease; impaired glucose tolerance; oral glucose tolerance test; maternal hyperglycemia

## Introduction

Congenital heart disease (CHD) is one of the most common congenital malformation, with a very broad spectrum. The incidence of CHD is subject to the definition, follow-up time, and inclusion criteria. A large study for prevalence and perinatal mortality, European Surveillance of Congenital Anomalies (EUROCAT), in 2000 to 2005 found that the prevalence of CHD was 8.0 per 1,000 births.(1) Interaction of multiple factors involving both genetic and non-genetic factors contributes to the pathogenesis of CHD. Most of these interacting factors take place within the fetal-placental-maternal "environment" in early pregnancy. Maternal diabetes mellitus (DM), has been known to be a teratogen in this period.(2, 3) The teratogenic effect of diabetes in early pregnancy could be explained by the high incidence of conotruncal septation and bulboventricular looping abnormalities.(4) Supporting this theory, increased incidence of cardiac malformation in the children of diabetic women was reported to be about 3-5%,(4-7) higher than the general population.

Elevated risk was also observed in mothers with gestational diabetes mellitus (GDM).[6] In addition, maternal hyperglycemia has been proposed to be the primary teratogen in diabetes and associated with higher incidence of CHD. The interrupted maternal metabolic state seemed to result in an accumulation of metabolic fuels that alter the expression of genes which control critical aspects of cardiac development.[4] Some studies also suggested that good glycemic control as a part of preconception care in pregnancies complicated by diabetes is effective in reducing congenital malformation, including CHD.[8, 9]

In view of the importance of good glycemic control in cardiac development, pregnant women with diabetes or unfavorable oral glucose tolerance test (OGTT) results should be given more attention in the fetal cardiac malformation screening. Cardiac screening as a part of prenatal diagnosis of CHD allows appropriate counseling for parents about prognosis, peri-partum management and referral to tertiary center for cardiac surgery which later improve survival and morbidity as well.[10] Combined and targeted ultrasound with indicated prenatal and postnatal echocardiography was suggested as an optimal strategy.[11] It is important to identify pregnancy with higher risk of CHD and should be referred to the cardiac screening. Therefore, a clinical paramater that can be used to predict the risk of CHD is needed.

The aims of this study are to evaluate the association between maternal antenatal OGTT and incidence of fetal CHD, and to determine whether maternal antenatal OGTT can be a predictor of fetal CHD in a tertiary maternity hospital.

## Materials and Methods

This is a retrospective study of 9,885 pregnant women who underwent First Trimester Screening (FTS) of Down syndrome in KK Women's and Children's Hospital (KKWCH), Singapore during the period of 1 January 2008 to 31 December 2009. Fifty-one fetuses with abnormal karyotypes and 549 multiple pregnancies were excluded from the study. Of the remaining 9,265 fetuses, there were 3,116 women who were indicated for one step 75-gram OGTT during 5-40 weeks of gestation. The indications for OGTT were: age above 35 years old; BMI more than 25 before pregnancy or at first booking visit; family history of diabetes in first degree relatives; past history of GDM, delivering macrosomic baby, having recurrent miscarriage or unexplained fetal death; current pregnancy was complicated with glycosuria, macrosomia, polyhydramnion, or recurrent urinary/genital tract infections. If a woman had multiple tests done during the study period, only the latest value between 18 to 30 weeks was included in the analysis. The OGTT results were classified according to the 2006 World Health Organization recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia (Table 1).[13]

Table 1. The 2006 World Health Organization recommendations for the diagnostic criteria of diabetes and intermediate hyperglycemia.

| Diagnosis | Blood Glucose Level (mmol/l) |
|---|---|
| Diabetes | Fasting ≥ 7.0 or 2-hours ≥ 11.1 |
| Impaired Glucose Tolerance | Fasting < 7.0 and 2-hours 7.8-11.0 |
| Impaired Fasting Glucose Tolerance | Fasting 6.1-6.9 and 2-hours <7.8 |

Continuous data were compared between the CHD and non-CHD group using Student's *t*-test, nominal variables were compared using Chi-square test or Fisher's exact test. A *p* value less than 0.05 was considered significant. The FGL and 2-HGL data were analyzed using a Receiver Operating Characteristic (ROC) curve.

Maternal characteristic and the prenatal diagnosis of CHD were obtained from the Birth Defect Registry, fetal characteristics at birth were retrieved from hospital medical records. Abnormalities in the four-chamber and outflow tracts that were found through FTS ultrasound scan at 11-13 week, cardiac scan at 14-16 weeks, detailed screening scan at 18-23 weeks, and/or subsequent follow-ups were determined as antenatal diagnosis of CHD. The postnatal diagnosis using fetal echocardiography up to the first month of life was stated whenever available.

**Results**

The maternal and neonatal characteristics of our subjects were described in Table 2. The mean maternal age, race, number of pregnancies and parity were comparable between the CHD and non-CHD groups ($p$>0.05). The distribution of the sex of the babies (54% vs 45%, $p$=0.99), as well as mean gestational age at delivery (38.3±1.2 vs 38.3±1.6, $p$=0.95) from both groups was also similar. Babies with CHD were slightly heavier at birth than those without CHD (3.3 kg vs 3.1 kg, $p$=0.17).

Table 2. Maternal and neonatal characteristics.

| | CHD (n=12) | Non-CHD (n=3104) | *p* |
|---|---|---|---|
| **Maternal** | | | |
| *Maternal age at FTS* | 33.5 ± 4.6 | 32.3 ± 5.6 | 0.38 |
| *Race* | | | |
| White | 1 (8.3%) | 17 (0.5 %) | 0.11 |
| Black | 0 (0%) | 1 (0.03 %) | |
| East Asian | 8 (66.7%) | 2028 (65.3 %) | |
| South Asian | 2 (16.7%) | 704 (22.7 %) | |
| Mixed | 1 (8.3%) | 354 (11.4 %) | |
| *Gravida* | 2.4±1.6 | 2.2±1.2* | 0.49 |
| *Parity* | 1.9±1.1 | 1.8±0.9* | 0.65 |
| **Neonatal**** | | | |
| *Sex* | | | |
| Male | 6 (54.6%) | 1476 (54.3%) | 0.99 |
| Female | 5 (45.5%) | 1243 (45.7%) | |
| *Gestational age at delivery* | 38.3±1.2 | 38.3±1.6 | 0.95 |
| *Birth weight* | 3,307.5±475.7 | 3,120.7±452.7 | 0.17 |

Race distribution: White (European, Middle Eastern, North African, Hispanic), Black (African, Caribbean, African, American), East Asian (Chinese, Korean, Japanese), South Asian (Indian, Pakistani, Bangladeshi), and Mixed.

* There were 385 missing data for gravida and parity.

** There were 1 MTPT without post mortem examination in the CHD group and 385 missing data for neonatal outcome in the non-CHD group.

Table 3 shows the FGL and 2-HGL profile in the CHD and non-CHD groups. The FGL and 2-HGL mean values were not significantly different between the two groups ($p$=0.20 and 0.84 respectively). Of the 3,116 mothers, there were 899 (28.85%) who had 2-HGL above 7.80 mmol/l, and thus classified according to 2006 WHO diagnostic criteria as having “impaired glucose tolerance”. There were no patient in our study who had overt diabetes.

Table 3. Antenatal fasting and 2-hours post load glucose profile of CHD and non-CHD group.

| | CHD ($n$=12) | Non-CHD ($n$=3104) | $p$ |
|---|---|---|---|
| Fasting (mmol/l) | 4.3 ± 0.2 | 4.5 ± 0.6 | 0.20 |
| 2-hours post load (mmol/l) | 6.9 ± 1.5 | 7.1 ± 1.8 | 0.84 |
| Gestational age at OGTT | 27.4±4.0 | 27.3±4.5 | 0.94 |

Table 4. Incidence of CHD according to glucose tolerance status.

| | IGT n (%) | Non-IGT n (%) | Total n (%) | $p$ |
|---|---|---|---|---|
| CHD | 4 (0.44) | 8 (0.36) | 12 (0.38) | 0.73 |
| Non-CHD | 895 (99.55) | 2,209 (99.64) | 3,104 (99.62) | |
| Total | 899 (100) | 2,217 (100) | 3,116 (100) | |

Twelve (0.38%) fetuses in our study were diagnosed with CHD antenatally by ultrasound (Table 4). The incidence of CHD was marginally higher in mothers with IGT compared to mothers without IGT (0.44% vs 0.36%, $p$=0.73). The description of antenatally diagnosed CHD cases and subsequent postnatal echocardiography findings are shown in Table 5.

Table 5. Antenatal and postnatal diagnosis of CHD.

| Case | Antenatal Ultrasound | Postnatal Echocardiography | FGL (mmol/l) | 2-HGL (mmol/l) |
|---|---|---|---|---|
| 1 | CoA, dilated RA, anomalous venous return to RA | Hypoplastic aortic arch, hypoplastic right PA & PV, large PDA (Congenital pulmonary agenesis, CDH) | 4.30 | 5.10 |
| 2 | FT, DORV | FT, DORV, ASD/PFO | 4.50 | 4.70 |
| 3 | TGA, DORV, PS, VSD | (MTPT) | 4.30 | 5.50 |
| 4 | TGA,VSD | TGA,VSD, ASD, PDA | 4.00 | 6.10 |
| 5 | TGA | TGA, PDA, ostium secundum ASD, PFO | 4.20 | 7.80 |
| 6 | VSD | VSD, PDA, ostium secundum ASD | 4.50 | 6.20 |
| 7 | VSD | VSD, ASD/PFO | 4.00 | 9.30 |
| 8 | VSD | Ostium secundum ASD | 4.20 | 6.80 |
| 9 | VSD | NA | 4.30 | 8.90 |
| 10 | VSD | NA | 4.30 | 8.80 |
| 11 | VSD | NA | 4.50 | 7.20 |
| 12 | VSD | NA | 4.00 | 7.00 |

ASD : atrial septal defect, CDH : congenital diaphragmatic hernia, CHD : congenital heart disease, CoA : Coarctation of aorta, DORV: double outlet of right ventricle, FT : Fallot's tetralogy, MTPT : Mid Trimester Pregnancy Termination, PFO : patent foramen ovale, PA : pulmonary artery, PDA : patent ductus arteriosus, PS : pulmonary stenosis, RA : Right atrium, TGA : transposition of the great arteries, VSD : ventricle septal defect

The ROC curve was plotted for each of the two antenatal OGTT results and superimposed on one graph, to compare the predictive value of CHD between the two predictors. All of the CHD cases could be detected (100% sensitivity) when FGL were above 4.0 mmol/l or 2-HGL more than 4.7 mmol/l, but the false positive rate were also high (88.9% and 95.4%, respectively). In addition, the areas under curve were 0.38 for FGL and 0.50 for 2-HGL. There appeared to be no ideal cut-off for the prediction of CHD using antenatal OGTT.

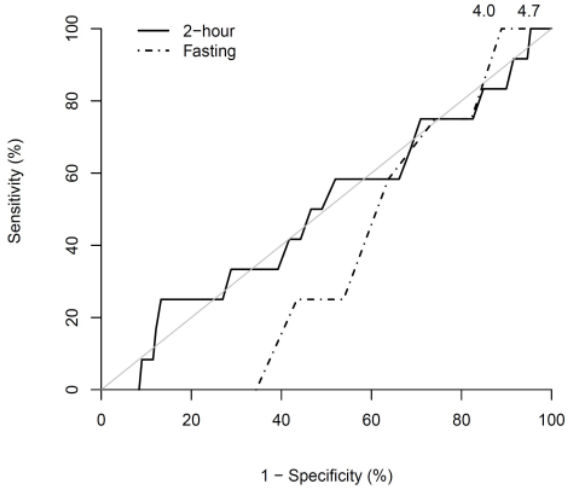


Figure 1. ROC curves for the prediction of CHD using fasting and 2-hours post load OGTT.

**Discussion**

Results from our study suggest that neither FGL nor 2-FGL appears to be useful in assessing the risk of CHD during pregnancy. Nonetheless, our interest in this topic stemmed from earlier reports on the observed higher incidence of CHD in women with DM (Table 6). Liveborn babies of mothers with type-1 DM were shown to be more likely to have CHD (3.6%-5%),[4-7] while in the GDM population the incidence of CHD (1.44%) was only slightly higher than general population.[6] However, in these studies there were no specifications of the exact diagnostic criteria of DM.

Table 6. Congenital heart disease in pregnancy complicated by diabetes.

| Author | Location | Publication Year | Diabetic Population | No. of Offspring (*n*) | CHD (*n*; %) |
|---|---|---|---|---|---|
| Aberg *et al*[6] | Sweden | 2001 | GDM | 8,688 | 125 (1.44%)[a] |
| Aberg *et al*[6] | Sweden | 2001 | Pre-existing diabetes | 3,864 | 158 (4.09%)[a] |
| Wren *et al*[5] | UK | 2003 | Pre-existing Diabetes | 192,618 | 22/609 (3.6%) |
| Abu Sulaiman and Subaih [25] | Saudi Arabia | 2004 | T1DM | 100 | 15 (15%)[b] |
| Lisowski *et al*[4] | US, The Netherlands | 2010 | T1DM (including multiple pregnancies) | 1,176 | 41 (3.5%) |
| Ulmo *et al*[7] | Switzerland | 2007 | T1DM, T2DM, GDM | 92 | 5 (5%) |

CHD : Congenital Heart Disease, T1DM : Type-1 Diabetes Mellitus, T2DM : Type-2 Diabetes Mellitus, GDM : Gestational Diabetes, PDA : Patent Ductus Arteriosus, HCM : Hypertrophy Cardiomyopathy

[a] Including specified and unspecified cardiac defect and PDA

[b] Excluding PDA & HCM

There are other publications that investigated the relationship between FGL and various types of congenital anomalies (CA-s). In a sub-population of 4,151 infants with major CA-s whose mothers had type-2 DM or GDM studied by Schaefer *et al*, the incidence of CHD was 0.77% in mothers with FGL above 6.7 mmol/l, and as high as 0.24% if cut-off above 11.1 mmol/l was used.[14] Moreover, the incidence of CHD was

1.41% in babies of GDM mothers with FGL above 7.2 mmol/l and/or 1-hour above 11.1 mmol/l.[12] In comparison, our finding suggested that all CHD cases would be detected using FGL more than 4.0 mmol/l (Fig.1) or 2-HGL above 4.7 mmol/l, however the false positive rate was also high (88.9% and 95.36%, respectively). As a result, we did not find an ideal cut-off above which the risk of fetal CHD was markedly elevated.

In this study, CHD was found in 0.44% of the IGT population (Table 4), close to the background incidence (0.38%). The two ROC curves corresponding to FGL and 2-FGL produced an Area Under the Curve of 0.38 and 0.50, respectively. Thus there is no conclusive evidence that either maternal antenatal fasting or 2-hours post load glucose could be useful in the risk evaluation of fetal CHD. This result is not surprising given that the mean glucose level values were not significantly different between the CHD and non-CHD group. The lack of association between glucose level values and the incidence of CHD was probably due to a small study sample with only 12 CHD cases and no overt diabetic patients.

In contrast to our findings, a cohort by Sermer *et al* studying 3637 patients did demonstrate the increasing carbohydrate intolerance in women without overt gestational diabetes, and showed that it was associated with a significantly increased incidence of cesarean sections, preeclampsia, macrosomia, and need for phototherapy, longer maternal and neonatal hospital stay.[15] A large-scale (25,000 pregnant women) multinational epidemiologic study, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, showed a continuous association between maternal glycemia at 24 to 28 weeks and the risk of adverse maternal, fetal, and neonatal outcomes, even within ranges that used to be counted as normal for pregnancy.[16] In view of the association between maternal glycemia and various adverse outcomes, The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended that all women without prior history of diabetes should undergo a 75-g OGTT at 24 to 28 weeks of gestation.[17]

Antenatal OGTT has not only been known as an important tool to detect hyperglycemia, but also useful to predict late-onset GDM,[18] postpartum glycemia and beta-cell dysfunction (postpartum pre-diabetes condition),[19] spontaneous abortion, and CA-s.[20] Hence, our study did not find that antenatal OGTT was useful in risk evaluation of CHD. Tan *et al* also evaluated that antenatal OGTT were not advantageous in predicting persistent postpartum abnormal glucose tolerance.[21] Savona Ventura *et al* did not find that third trimester OGTT was beneficial to predict increasing risk of hypertension, obstetric intervention, respiratory distress, macrosomia, and associated shoulder dystocia.[22]

As commonly suggested, early prenatal diagnosis of congenital heart anomalies in women with diabetes is warranted using detailed ultrasound examination, and fetal echocardiography.[23] Although our result indicated no association, we need to be aware that maternal hyperglycemia has been proposed to be the primary teratogen in diabetes.[24] Good glycemic control as primary prevention of CHD related to maternal hyperglycemia should be emphasized in the counselling of every women of child-bearing age. Larger studies that include more clearly defined diabetes patients and larger number of CHD cases might yield more conclusive findings.

Although the incidence of CHD was slightly higher in pregnancies complicated with IGT (0.44%) compared to all study population (0.38%), this unsignificant finding might be a result of the absence of overt diabetes patients and the small number of CHD cases in our study. We could not recommend a cut-off for FGL or 2-HGL above which a pregnant woman should be selectively referred for fetal cardiac screening. Diabetes or elevated glucose level alone might not be an indication for fetal heart anomalies assessment. Further study may be needed to confirm our findings.

**Conclusion**

We found that there were no significant differences in maternal and neonatal characteristics, mean glucose levels and incidence of maternal IGT between the CHD and non-CHD groups. Meaningful OGTT value above which the risk of CHD increased dramatically could not be determined. Neither fasting nor 2-hours post load glucose values of maternal antenatal OGTT appeared to be a predictor of fetal CHD. Therefore we suggested that there were no association between antenatal OGTT and the incidence of CHD.

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