A Study Of The Impact Of Carrying 'Xy Chromosome' On Maternal Insulin Secretion And Insulin Resistance At A Tertiary Care Center In Chennai.

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Abstract

Background: Retrospective analyses of perinatal databases have raised the suspicion that there could be a positive association between the fetal gender and gestational diabetes mellitus (GDM), but it is still unclear. We thus thought to evaluate the relationship between fetal sex and maternal glucose metabolism in a well-characterized cohort of women reflecting the full spectrum of GDM in a prospective cohort study.

Research Design & Methods: It is a prospective cohort study with 104 pregnant women with GDM diagnosed by Diabetes in Pregnancy Societies of India (DIPSI) guidelines were selected for the study. Maternal BMI, and mode of treatment given for GDM was noted along with baby's birth weight and gender. Clinical risk factors were compared between women carrying a female fetus (n = 52) and those carrying a male fetus (n = 52).
Statistical Analysis: GDM mother's glucose challenge test (GCT) values, mode of treatment of GDM mothers, baby birth weight, maternal body mass index (BMI) at term, and mode of delivery were expressed in percentage. A Chi-square test was used to estimate the association between the maternal GCT values versus fetal gender and fetal gender versus mode of maternal treatment, using SPSS 21.0 version.

Results: Women carrying a male fetus had a poorer β-cell function and higher range of GCT values as compared with those carrying a female fetus. Furthermore, women carrying a male fetus had higher proportions of developing GDM and its complications.

Conclusion: Male fetus is associated with poorer β-cell function, higher GCT values and an increased risk of GDM in the mother. Thus, fetal sex potentially may influence maternal glucose metabolism in pregnancy.

Keywords: Male fetus, GDM, insulin resistance, poor β – cell function, Diabetes in Pregnancy Societies of India

INTRODUCTION

GDM is the condition characterized by the inability of the pancreatic β – cells to secrete sufficient insulin, which in turn fails to combat the physiological insulin resistance during late pregnancy leading to hyperglycemia [1]. The existence of a gender difference in maternal GDM appears to be universal suggesting that its mechanism is likely to be of fundamental importance [2]. Fetal gender in utero plays an important role in perinatal morbidity and mortality. It has been thought that pregnant women carrying male fetuses are at increased risk of poorer maternal β-cell function which is the main pathophysiology in gestational diabetes mellitus (GDM) and progression to type 2 DM in the future as in many women with GDM pancreatic β – cell function begins to decrease within the first year postpartum and continues to decline thereafter every year [3]. It was also thought that a male fetus carries increased risks of maternal perinatal outcomes including fetal macrosomia leading to assisted vaginal delivery, higher cesarean section rates, non-reassuring fetal heart

rate patterns, non- progression of labor, premature rupture of membranes, preterm delivery, and umbilical cord prolapse. Women with gestational diabetes carrying the male fetus had poorer glucose tolerance and were on higher rates of insulin therapy compared to other treatment modalities [4].

This mechanism by which how the male fetus contributes to the poorer maternal β-cell function is still unclear. As there is a dearth of knowledge about this ill defined area, we planned to evaluate the association between fetal sex on maternal insulin secretion and insulin resistance.

AIM:

The aim of this study is to determine the impact of fetal sex on maternal insulin secretion and insulin resistance and it's sequelae.

STUDY DESIGN:

Prospective cohort study (May 2019 – August 2020). Data collected at Chettinad Hospital & Research Institute, Kelambakkam – 603103. The study was started after getting Institutional Human Ethics Committee clearance.

SAMPLE SIZE:

A convenience sampling method was used, and 104 GDM women were selected for the study.

MATERIALS AND METHOD:

1) Information regarding the project was briefed to the GDM women and their families.
2) Informed consent was obtained.
3) Pregnant women who were already diagnosed as GDM by DIPSI guidelines were recruited for the study.

DIPSI (Diabetes in Pregnancy Societies of India):

- It is a single-step procedure.
- 75 gm of oral glucose was given irrespective of the time of the last meal.
- venous plasma glucose value at 2-hour more than 140 mg/dl was diagnosed as GDM [5].

4) Plasma glucose estimation in the mother's blood sample was done by the **Hexokinase method** in **SIEMEN'SDIMENSION RxLMACHINE** immediately after centrifugation.
5) Sex of the fetus is noted after birth.

INCLUSION CRIETERIA:

1) Pregnant women between 18- 45years,
2) GDM confirmed between 24-28 weeks (GCT),
3) All GDM women were included.

EXCLUSION CRITERIA:

1) Previously known case of DM,
2) Major medical or surgical history in the past,
3) Anomalous fetus in present pregnancy,
4) PIH / Pre-eclampsia / Eclampsia.

STATISTICAL METHOD:

GDM mothers' GCT values, mode of treatment of GDM mothers, baby birth weight, maternal BMI at term, and mode of delivery were expressed in percentage. A Chi-square test was used to estimate the association between the maternal GCT values versus fetal gender and fetal gender versus mode of maternal treatment, using SPSS 21.0 version.

RESULTS AND ANALYSIS

In the study 5.8 % of GDM women who delivered male babies had GCT values between 160- 170 mg/dl, 28.8 % had values between 171 – 180 mg/dl, 65.4 % had values > 181 mg/dl. And 26.9 % of GDM women who delivered female babies had GCT values between 140 – 150 mg/dl, 65.4 % had values between 151 – 160 mg/dl and 7.7 % had values between 161 – 170 mg/dl. The inference is that a greater percentage of GDM women who delivered male babies had much higher values of GCT when compared to GDM women who delivered female babies.

Fig 1. Distribution of GCT Values In GDM Women Who Delivered Male Fetus.

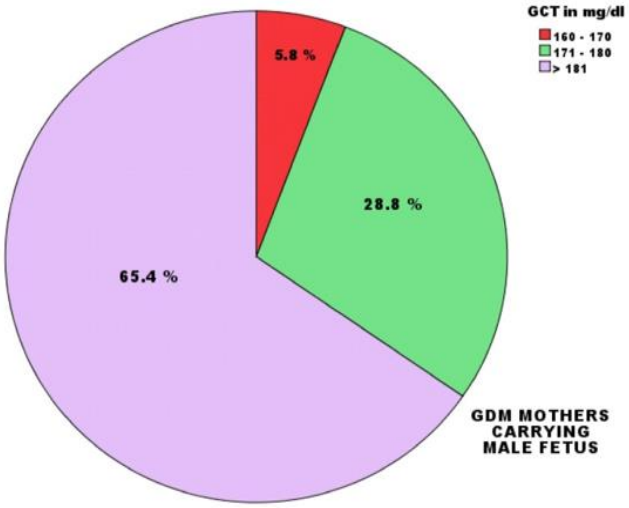
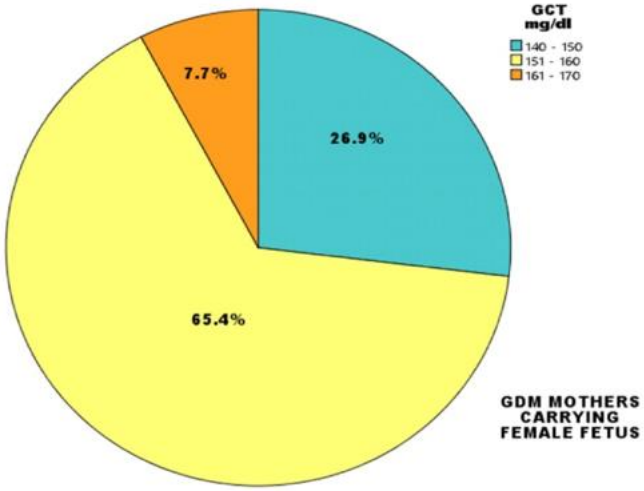


Fig 2. Distribution Of GCT Values In GDM Women Who Delivered Female Ferus.



Among the treatment type, 33 % of GDM women who delivered male babies were treated with diabetic meal plans, 53.8 % were treated with insulin and 13.2 % were treated with tablet metformin. And 78.3 % of GDM women who delivered female babies were treated with a diabetic meal plan, 6.7 % were treated with insulin and 15 % were treated with tablet metformin. This indicates that the majority of GDM women who delivered male babies required Insulin but majority of DM women who delivered female babies were treated with a diabetic meal plan only.

Fig 3. Distribution Of Treatment Type In GDM Women Who Delivered Male Fetus

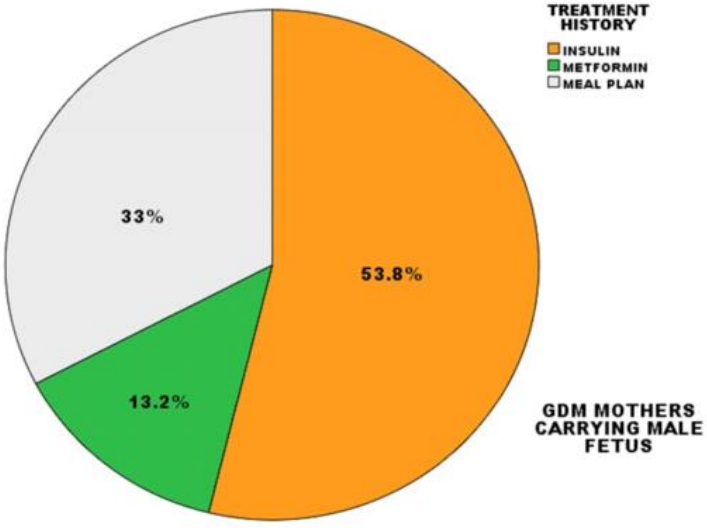
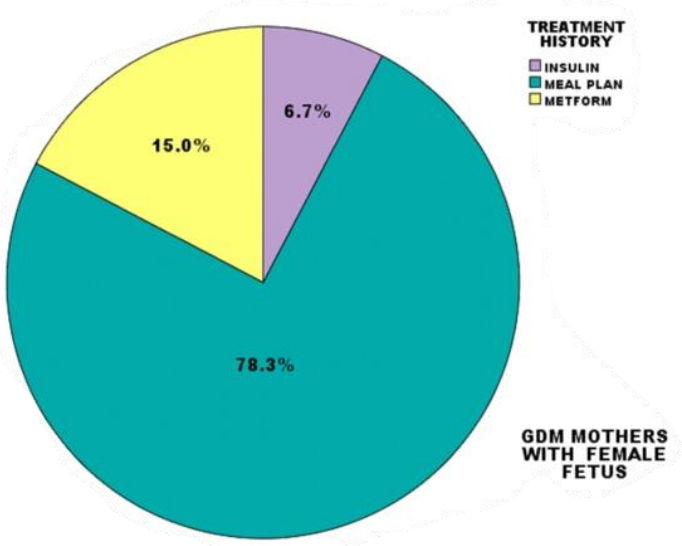


Fig 4. Distribution Of Treatment Type In GDM Women Who Delivered Female Fetus



Taking into consideration, the birth weight 67.3 % of male babies were > 3.5 kgs and 32.7 % were < 3.5 kgs, while 25.1 % of female babies were > 3.5 kgs and 74.9 % were < 3.5 kgs.

Table 1. Distribution Of Birth Weight In Kgs In GDM Women Who Delivered Male And Female Babies

WEIGHT IN Kgs	MALE BABIES	FEMALE BABIES
> 3.5	67.3 %	25.1 %
< 3.5	32.7 %	74.9 %

The BMI in 73.1 % of GDM women who delivered male babies were > 30 kg/m^2 and 26.9 % were < 30 kg/m^2, while 52.7 % of GDM women who delivered female babies were > 30 kg/m^2 and 47.3 % were < 30 kg/m^2. These results show higher birth weight and BMI among women who delivered male babies.

Table 2. Comparison Of Maternal BMI In Kg/m^2 In GDM Women Who Delivered Male And Female Fetus

MATERNAL BMI AT TERM (Kg/m^2)	MALE BABIES	FEMALE BABIES
>30	73.1 %	52.7 %
<30	26.9 %	47.3 %

The mode of delivery was as follows. 23.1 % of GDM women who delivered male babies had a normal vaginal delivery, 25.0 % had an operative vaginal delivery and 51.9 % had cesarean delivery while 65.1 % of GDM women who delivered female babies had a normal vaginal delivery, 5.8 % had an operative vaginal delivery and 29.1 % had cesarean delivery. The requirement of caesarean section is higher in GDM women who delivered male babies.

Table 3. Distribution Of Mode Of Delivered In GDM Women Who Delivered Male And Female Fetus

MODE OF DELIVERY	MALE BABIES	FEMALE BABIES
NORMAL VAGINAL DELIVERY	23.1 %	65.1 %
OPERATIVE VAGINAL DELIVERY	25.0 %	5.8 %
CESAREAN SECTION	51.9 %	29.1 %

Chi square test was done was used to determine the association between the maternal GCT values and fetal gender.This association was statistically significant with p value < 0.001*. Out of 52 GDM women who carried male fetus 48

women had GCT values >160 mg / dl and 4 women had GCT values < 160 mg/dl. Out of 52 women who carried female fetus 36 women had GCT values < 160 mg/dl and 16 women had GCT values > 160 mg/dl.

Table 4. CHI Square Test – Association Between GCT Values And Fetal Gender

GCT mg/dl	MALE FETUS	FEMALE FETUS
< 160	4	36
> 160	48	16

DISCUSSION:

The sex of a baby has been associated with the risk of adverse obstetrical outcomes at delivery. Indeed, carrying a male fetus confers increased risks of multiple adverse perinatal outcomes including premature rupture of membranes, pre-term delivery, failure to progress in the first and second stages of labor, non-reassuring fetal heart rate patterns, umbilical cord prolapse, true umbilical cord knot, Caesarean delivery, and lower Apgar scores [6,7]. However, it has traditionally not been suspected that the sex of the fetus could hold implications for maternal glucose metabolism. Intriguingly, it was recently demonstrated that, when compared with those carrying a girl, women carrying a male fetus have poorer pancreatic beta cell function in pregnancy, higher postprandial glycemia, and an elevated risk of GDM, independent of classical diabetes risk factors [3]. Furthermore, in women who develop GDM, the sex of the baby is a predictor of the mother's risk for early postpartum progression to type 2 diabetes after delivery [1]. For the normal maintenance of glucose homeostasis during pregnancy, the maternal β-cells should secrete more insulin to compensate for the severe acquired insulin resistance during late gestation which is thought to be due to the counter-regulatory hormones like human placental lactogen (HPL) and prolactin secreted by the placenta. Previous studies have shown a differential level of HPL and prolactin with respect to gender i.e., male fetuses produce an increased concentration of these hormones into circulation compared to the female fetus [8,9].

The paternal HLA genotypes expressed by the fetus (through the transmission of the paternal genes to the fetus) play an important role in affecting the maternal metabolism during pregnancy to boost fetal growth by increasing nutrient availability and increasing the risk of GDM [10]. The food intake is 10% higher in pregnant women carrying a male fetus compared to a woman carrying a female fetus [11]. In a common population, the birth weight of male offsprings are high when compared to female babies can be explained by the above phenomenon. Among women whose first pregnancy was complicated by GDM, fetal sex in the second pregnancy was not associated with the recurrence of GDM whether the mother had delivered a boy in her first pregnancy or a girl. In women who had a non-GDM first pregnancy with a male baby, having a boy in the second pregnancy was associated with the risk of GDM at only borderline significance. Among women with a non-GDM first gestation while carrying a girl, having a boy in their next pregnancy predicted an increased risk of GDM in that pregnancy. Thus, the sex of the baby in a non-GDM first pregnancy can hold implications for the association between fetal sex and the risk of GDM in the second pregnancy. In a large retrospective analysis of 1,08,995 deliveries in Israel done by Sheiner et al., 5,994 deliveries in the United States done by Di Renzo et al., 29,530 deliveries in Spain done by Aibar et al., 28,140 deliveries in Libya done by Khalil t al. found that the prevalence of GDM is more in women carrying male fetus compared to women carrying a female fetus. Though maternal physiology can affect the fetal metabolism in utero and is well recognized, our study reveals that there is a bidirectional association between the mother and the fetus where the fetus can affect the maternal metabolism leading to increased energy consumption in the mother and leading to GDM [10]. This effect is more pronounced in a woman carrying a male fetus.

CONCLUSION

The current study demonstrates the impaired post-challenge glycemic response to a physiological load of oral glucose finally leading to increased severity of GDM in the presence of a male fetus.

STRENGTH OF THE STUDY

1. Prospective cohort study
2. Only the GDM group were taken up for the study

LIMITATIONS OF THE STUDY:

1. Limited sample size,
2. Correlation between maternal and fetal parameters can be considered in future,
3. In a country like India, the sex of the baby is not revealed during pregnancy to create awareness of the risk and severity of GDM in early pregnancy.

CLINICAL SIGNIFICANCE

A careful watch on mothers carrying the male fetus is necessary in order to prevent the severity of GDM through early diet and physical activity.

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