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## RESEARCH ARTICLE

# RELATIONSHIP BETWEEN FERTILITY HORMONES AND GLYCATED HAEMOGLOBIN IN TYPE 2 DIABETIC SUBJECTS

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**ABSTRACT**

Diabetes Mellitus is a metabolic disorder and may result into hormonal imbalance which may lead to infertility. In the recent time, female infertility has become one of the chronic effects of Diabetes Mellitus. The study aimed at evaluating the fertility hormones and glycated haemoglobin in type 2 diabetic females. A total of one hundred and eighty subjects (90 Type 2 diabetic females and 90 apparently healthy females) within age 20 -50 years were investigated. Blood specimen was collected from the subjects for the determination of fasting plasma glucose, glycated haemoglobin (HBA1c) and fertility hormones on the 3rd day of the menstrual cycle. Fasting plasma glucose was determined spectrophotometrically using glucose oxidase method; HBA1c was determined using automated boronate affinity assay method while the fertility hormones were determined using Enzyme Linked Immunosorbent Assay (ELISA) method. The results showed significant decrease ($p<0.05$) in the levels of FSH, LH, prolactin in the type 2 DM subjects compared with the control subjects while HBA1c and Estradiol showed significant increase ($p<0.05$). There were significant negative relationships between HBA1c and fertility hormones in type 2 DM. The findings suggest that uncontrolled and persistent hyperglycaemia can predispose Type 2 diabetic females to fertility hormone imbalance.



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## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder and may result into hormonal imbalance which may lead to infertility. The prevalence rate of diabetes in Africa has been shown to be approximately 14.7 million adults in 2010, with a regional prevalence of 3.8%. Nigeria has the largest number in Africa which is approximately 1.7 million and the figure is expected to increase to 4.8 million by the year 2030 (WHO, 2010). Infertility risk factors associated with diabetes mellitus include hormonal imbalance, menstrual abnormalities, sexual dysfunctions, and shortening of reproductive period (Anna, 2009). Type 2 DM can be regarded as a disorder of both insulin resistance and relative insulin deficiency (Kumar, 2005 and Wendy, 2007). This class of diabetes mellitus has been shown to comprise approximately 90% of all cases of DM (Carl, 2010). Female infertility has become one of the chronic effects of DM in the recent time.

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It has been shown that there is an association between type 2 diabetes and fertility, alterations in the length of the menstrual cycle and the menopause age of onset. Furthermore, insulin resistance, obesity and diabetes mellitus has been shown to strongly correlate with polycystic ovarian syndrome (PCOS) (Van Der *et al.*, 2007). This association has not been investigated in the study area. Therefore, the study evaluated whether there is significant relationship between the levels of Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Prolactin, Glycated Haemoglobin (HBA1c) and Fasting Plasma Glucose (FPG) levels on day 3 (follicular phase) of the menstrual cycle since fertility in female is dependent on normal phases of the menstrual cycle. The study also looked at some vital signs such as body mass index, systolic and diastolic blood pressure since they have been shown to be risk factors in DM.

## MATERIALS AND METHODS

The study involved 180 subjects; Type 2 diabetic female subjects and 90 apparently healthy non-diabetic females which

served as control. The subjects were randomly recruited for the study. The subjects were on metformin (500mg-2.5g daily) and glibenclamide (5mg-20mg daily). Anthropometric measurements were taken using standard instrument. Height and weight were taken by one observer. Body mass index (BMI in Kg/m²) was calculated by dividing the weight in kilogram by the square of height. Systolic (SBP) and diastolic (DBP) blood pressures (mmHg) were also taken while subjects were at rest. Blood specimen was collected from the subjects for the determination of fasting plasma glucose concentration which was analyzed using glucose oxidase method (Trinder, 1969).

The hormones were analyzed using ELISA technique [follicle stimulating hormone (Marshal, 1975), lutenizing hormone (Uotilam 1981), estradiol (Tsang, 1989) were analyzed using ELISA technique while glycated haemoglobin was analyzed using boronate affinity assay (Nathan, 1984). Statistical Package for Social Science (SPSS) version 20.0 was used for the analysis of the results obtained. Data collected was subjected to statistical analysis using student t-test and correlation (r). Values were deemed significant at $p<0.05$.

## RESULTS

The report on Table 1 shows significant increase in the levels of BMI, SBP and DBP between the diabetic and control subjects. There was no significant difference in the ages of the diabetic subjects compared with the control subjects. Table 2 showed significant decrease in the mean levels of FSH (miu/ml), LH (miu/ml) and prolactin (ng/ml) but a significant increase in Estradiol (pg/ml) in type 2 DM compared with control subjects. In table 3, there was a significant negative correlation between BMI and FSH, LH, prolactin and estradiol levels ($P < 0.05$) in diabetic subjects.

**Table 1. Anthropometric data in Type 2 DM and Control subjects**

| Parameters | Diabetic subjects | Control | t value | P value |
|---|---|---|---|---|
| Age (years) | 38.92±5.54 | 38.30±6.05 | 0.7190 | 0.4730 |
| BMI (kg/m²) | 33.41±4.87 | 26.53±1.89 | 12.4920 | 0.0000* |
| SBP (mmHg) | 129.81±10.95 | 123.87±5.51 | 4.6010 | 0.0000* |
| DBP (mmHg) | 82.44±7.65 | 78.72±5.00 | 3.8620 | 0.0000* |

n=90
* significant at $P < 0.05$

**Table 2. FPG, HBA1c and fertility hormones in Type 2 DM and control subjects**

| Parameter | Diabetic subjects | Control | t value | P value |
|---|---|---|---|---|
| FPG (mmol/l) | 7.50±1.83 | 4.58±0.42 | 14.7620 | 0.0000* |
| HBA1c (%) | 7.44±0.48 | 4.80±0.62 | 31.8350 | 0.0000* |
| FSH (miu/ml) | 4.63±1.62 | 10.40±2.19 | -20.1120 | 0.0000* |
| LH (miu/ml) | 7.53±1.87 | 17.08±3.77 | -21.5060 | 0.0000* |
| Prolactin (ng/ml) | 8.12±1.35 | 13.53±3.98 | -12.2100 | 0.0000* |
| Estradiol (pg/ml) | 41.73±6.88 | 38.43±4.85 | 3.7180 | 0.0000* |

n=90
* significant at $P < 0.05$

**Table 3. Relationship between fertility hormones and anthropometric data in Type 2 DM and control subjects**

| Parameters | | Age (years) | | BMI (kg/m²) | | SBP (mmHg) | | DBP (mmHg) | |
|---|---|---|---|---|---|---|---|---|---|
| | | R | P | R | P | R | P | R | P |
| FSH | Diabetic | -0.16 | 0.12 | -0.71 | 0.00* | -0.19 | 0.07 | -0.12 | 0.25 |
| | Control | -0.02 | 0.88 | 0.06 | 0.60 | -0.02 | 0.87 | 0.01 | 0.95 |
| LH | Diabetic | -0.15 | 0.15 | -0.59 | 0.00* | -0.05 | 0.65 | -0.08 | 0.45 |
| | Control | 0.03 | 0.75 | 0.09 | 0.38 | -0.02 | 0.89 | 0.05 | 0.67 |
| Prolactin | Diabetic | 0.11 | 0.29 | -0.28 | 0.01* | -0.10 | 0.34 | -0.06 | 0.59 |
| | Control | -0.17 | 0.11 | -0.12 | 0.25 | 0.12 | 0.88 | 0.07 | 0.51 |
| Estradiol | Diabetic | -0.21 | 0.05* | -0.42 | 0.00* | 0.06 | 0.59 | 0.13 | 0.22 |
| | Control | -0.02 | 0.82 | -0.11 | 0.32 | 0.15 | 0.16 | 0.16 | 0.14 |

n=90
* significant at $P < 0.05$

**Table 4. Relationship between Fertility hormones, FPG and HBA1c in Type 2 DM and control subjects**

| Parameters | | FPG (mmol/l) | | HBA1c (%) | |
|---|---|---|---|---|---|
| | | R | P | R | P |
| FSH | Diabetic | -0.74 | 0.00* | -0.55 | 0.00* |
| | Control | 0.02 | 0.88 | -0.00 | 0.98 |
| LH | Diabetic | -0.58 | 0.00* | -0.43 | 0.00* |
| | Control | 0.01 | 0.91 | 0.01 | 0.94 |
| Prolactin | Diabetic | -0.28 | 0.01* | -0.10 | 0.34 |
| | Control | -0.00 | 0.97 | -0.06 | 0.55 |
| Estradiol | Diabetic | -0.35 | 0.00* | -0.26 | 0.02* |
| | Control | -0.19 | 0.08 | 0.03 | 0.79 |

n=90
* significant at $P < 0.05$

In table 4; FSH, LH, prolactin and Estradiol had significant negative correlations with FPG while FSH, LH and estradiol have significant negative correlation with HBA1c ($P < 0.05$) respectively in the diabetic subjects while the controls had none.

## DISCUSSION

Evaluation of fertility hormones (FSH, LH, prolactin, estradiol), fasting plasma glucose (FPG), glycated

haemoglobin (HBA1c) were carried out in type 2 DM and control female subjects on day 3 of their menstrual cycle. Increased levels of fasting plasma glucose and glycated haemoglobin were observed in the type 2 DM subjects compared with control. Both FPG and HBA1c can significantly affect the female fertility hormone balance. Body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also monitored in the subjects. In this study, BMI and blood pressure in Type 2 DM subjects were significantly increased compared with that of the control subjects. This is in line with a work which showed that BMI was significantly higher in women with type 2 DM than in controls (Mazzilli, 2015). The reason for the increase may be because increased BMI and blood pressure have been shown to be risk factors for the development and complications of many diseases including diabetic mellitus. The levels of FSH, LH and prolactin were significantly decreased in DM subjects compared with controls. This agreed with an earlier study carried out on evaluation of ovarian reserve function based on hormonal parameters in women with type 2 diabetes mellitus (Isik, 2012). Several authors have investigated sexual dysfunction in diabetic females and concluded that type 2 DM negatively affects female sexuality (Erol, 2002; Olarinoye, 2008; Ogbera, 2009). In these diabetic subjects, there were significant negative correlations (inverse relationship) between the levels of FPG and FSH, HBA1c and FSH, BMI and FSH which are in line with earlier works (Anna, 2009; Isik, 2012; Jensen, 1999; Norman, 2001; Codner, 2012). Also, there were significant negative correlations between the levels of FPG and LH, HBA1c and LH, BMI and LH. Furthermore, there were significant negative correlations between the levels of FPG and prolactin, BMI and prolactin whereas there was no significant correlation between the levels of HBA1c and prolactin, SBP and prolactin, DBP and prolactin, age and prolactin. This finding also support the study which stated that there is an association between type 2 diabetes and alterations in the length of reproductive age (Van Der, 2007). There were significant correlations between the levels of FPG and estradiol, HBA1c and estradiol, BMI and estradiol, age and estradiol in diabetic subjects. The findings of significant correlations as observed in this study are also in line with other works (Anna, 2009; Isik, 2012). The negative correlations (relationship) as observed in this study means that as the FPG and HBA1c are increasing, the fertility hormones are affected and as a result there is decrease in the secretion of the hormones. However, there was no significant correlation between age and the fertility hormones in both the diabetic subjects and controls except estradiol which showed negative correlation with age in diabetic subject.

**Conclusion**

In this study, it was observed that uncontrolled and elevated fasting blood glucose can significantly affect the female fertility hormone balance as evidenced in the decreased levels of FSH, LH and prolactin whereas there were significant increases in the levels of HBA1c and estradiol. Thus, significant negative correlation (inverse relationship) exists between HBA1c and fertility hormones in type 2 DM under study.

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