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GENERAL GYNECOLOGY

Beta-cell dysfunction and abnormal glucose metabolism among non-diabetic women with recurrent miscarriages

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Abstract

Background Subclinical beta-cell (β-cell) dysfunction is an endocrine abnormality and its association with recurrent miscarriages (RM) has not been extensively studied.

Objective This study aimed to determine the prevalence of β-cell dysfunction and abnormal glucose metabolism [fasting blood glucose (FBG) ≥ 5.1 mmol/L] among non-diabetic women with recurrent miscarriages and to establish if there was an association between RM and β-cell dysfunction and FBG ≥ 5.1 mmol/L.

Methodology This was a cross-sectional study involving 80 women with miscarriages at ≤ 13 weeks gestation and 80 women with normal pregnancies at ≤ 13 weeks of gestation with at least one successful live-birth and no history of miscarriage (comparison group). Interviewer-administered questionnaire was used to obtain relevant information. From each participant, FBG and fasting insulin were assayed. β-Cell function was computed. The data obtained was analysed using IBM-SPSS version 22.0.

Results A significantly higher prevalence of β-cell dysfunction and abnormal glucose metabolism were observed among non-diabetic women with RM compared to age-matched controls (38.8% vs 10.0%, $P < 0.001$) and (27.5% vs 6.3%, $P = 0.005$) respectively. The mean β-cell function of the cases was 59.0% of the controls (264.41 ± 105.13 vs 447.82 ± 181.24, $P < 0.001$). Mean FBG was significantly higher in the case-group compared to the controls (4.77 ± 1.14 mmol/L vs 3.58 ± 0.78 mmol/L, $P < 0.001$). There was a significant association between RM and FBG ≥ 5.1 mmol/L and low β-cell function ($P < 0.001$).

Conclusion This study suggests that women with recurrent miscarriages are more likely to have impaired β-cell function and abnormal glucose metabolism (FBG ≥ 5.1 mmol/L).

Keywords β-Cell dysfunction · Abnormal glucose metabolism · Recurrent miscarriages

Introduction

There is a complex relationship between beta-cell (β-cell) dysfunction and insulin insensitivity. In the presence of β-cell dysfunction, insulin secretion is impaired. Insulin insensitivity on the other hand implies that there is secretion of insulin but there is insulin resistance in target tissues [1]. Beta-cell dysfunction is a more severe abnormality than insulin resistance [1]. β-Cell dysfunction results from insufficient glucose sensing to stimulate insulin secretion leading to sustained elevated glucose concentrations. Sustained elevated glucose concentrations above the physiological range result in the manifestation of hyperglycaemia. In insulin-resistant state, insulin signalling within glucose recipient tissues is defective therefore hyperglycaemia persists. Both pathological states induce hyperglycaemia and therefore

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increase insulin demand. β-Cell dysfunction supersedes insulin resistance in inducing diabetes or diabetes-like state [1, 2]. Both abnormal states influence each other and presumably synergistically herald the onset of type 2 diabetes [2, 3].

Hyperglycaemia, a hallmark of abnormal glucose metabolism, is an important cause of both maternal and foetal complications in pregnancies. Hyperglycaemia interferes with implantation by inhibiting trophectoderm differentiation [4, 5]. It increases oxidative stress affecting the expression of critical genes essential for embryogenesis [4, 6, 7]. Hyperglycaemia promotes miscarriages by facilitating premature programmed-cell death of key progenitor cells of the blastocyst [4, 8]. Sustained hyperglycaemia is one of the cardinal findings in established diabetes mellitus. Therefore subclinical beta-cell defects in women without established diabetes mellitus may be injurious to early pregnancy as in the case of confirmed diabetes.

Although type 2 diabetes has been traditionally understood as a metabolic disorder initiated by insulin resistance, it has recently become apparent that impairment in insulin secretion contributes to its manifestation and may play a role in its early pathophysiology [9]. In normal physiological conditions, normoglycaemia is maintained under a balance between insulin sensitivity and insulin secretion and when insulin sensitivity decreases, insulin secretion increases to maintain normoglycaemia. Thus, insulin secretion should always be assessed in relation to insulin sensitivity [6]. Conservation of β-cell function and insulin signalling in β-cells and insulin signalling in the glucose recipient tissues will maintain glucose homeostasis.

Management of recurrent miscarriages (RM) is challenging for the couples and the clinicians because in 50% of the cases, no cause is identified [10]. This has made RM a topical issue for researchers. Up to 75% of fertilized ova and at least 15% of clinically recognized pregnancies never survive to birth [11]. Recurrent miscarriages (RM) affect about 2–4% of reproductive age couples [12]. It affects both naturally conceived pregnancies and pregnancies achieved after assisted reproductive technology treatment [13]. A number of endocrine-related factors have been implicated as causes of recurrent miscarriages but the role of subclinical beta-cell dysfunction has not been extensively studied. Beta-cell dysfunction even in subclinical level leads to some sort of abnormal glucose metabolism (hyperglycaemia) which is the major metabolite leading to adverse pregnancy outcome in known diabetics [14, 15].

We aimed to determine the prevalence of β-cell dysfunction and prevalence of abnormal glucose metabolism (FBG $\geq$ 5.1 mmol/L) [16] among non-diabetic women with first trimester recurrent miscarriages. It also sought to determine the relationship between recurrent first trimester miscarriages and β-cell dysfunction and abnormal glucose metabolism.

Material and methods

Study areas

This was a multicentre study conducted at the Jos University Teaching Hospital (JUTH), Plateau State Specialist Hospital (PSSH), and Fertile Ground Hospital/IVF-ET services (FGH). JUTH and PSSH are tertiary health institutions and FGH is a private facility, all located in Jos, the capital of Plateau State in North Central Nigeria. They offer services to patients from Plateau state and receive referrals from neighbouring states including Benue, Nasarawa, Kogi, Adamawa, Taraba, Bauchi, Gombe, and parts of Kaduna and Niger states.

Study design

This was a comparative cross-sectional study.

Study population

The study population comprised all eligible consenting women with history of recurrent first trimester miscarriages seen at the gynaecological unit of JUTH, PSSH, and FGH. The second (comparison) group comprised consenting pregnant women in the first trimester who presented for antenatal care booking during the study period. Excluded from this study were women who declined consent, women with previous pregnancy losses attributable to known causes, known diabetics, women with other forms of gestations (ectopic, molar), and women with diagnosis of polycystic ovary syndrome (PCOS). PCOS status was determined based on the revised Rotterdam criteria: (1) oligo- and/or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, and (3) polycystic ovaries with exclusion of other aetiologies (congenital adrenal hyperplasia, androgen secreting tumours or Cushing's syndrome). The diagnosis was made if any two out of the three criteria were met.

Pregnancy was defined based on ultrasound documentation of intrauterine gestation or presence of normal trophoblastic tissues on histological examination of evacuated uterine specimens. Recurrent first trimester pregnancy loss was defined as two or more spontaneous miscarriages occurring on or before 13 weeks of gestation in women with normal hormonal assay (prolactin, progesterone, testosterone, and thyroid function test), hysterosalpingogram or hysteroscopy, and pelvic scan. Gestational age was determined by ultrasound dating.

Ethical approvals were obtained from the Research and Ethical Committees of the Jos University Teaching Hospital, Plateau State Specialist Hospital and Fertile Ground Hospital.

Estimation of sample size

The sample size was estimated using the formula;

$$n = \frac{\{P1\ (1-P1)\ +\ P2\ (1-P2)\}\ \times\ (Z\ \alpha\ +Z\ \beta)^2}{(P1-P2)^2},$$

where n is the number of sample size in each of the group, $P1$ is the proportion of insulin resistance among women with recurrent miscarriage (0.24 in a similar study) [17], $P2$ is the proportion of insulin resistance among normal pregnant women with no history of miscarriage (0.08 in the same study) [17], $Z - \alpha/2$ is the value of standard normal distribution corresponding to a significant level of alpha (1.96 for two-sided test at the 0.05), $Z - \beta/2$ is the value of standard normal distribution corresponding to the desired level of power (0.84 for a power of 80%)

$$n = \frac{\{(0.24 \times 0.76 + 0.08\ \times\ 0.92)\} \times (1.96\ +\ 0.84)^2}{(0.16)^2}$$

$N \approx 78$, the sample size was adjusted to 80 for the cases and 80 for the controls (comparison group).

Data collection

Eighty cases and controls each were recruited for the study over a period of one and half years by consecutive sampling technique. Women with recurrent first trimester miscarriages were recruited into the case-group, while the control group comprised women within the same age range (±1) with at least one successful live-birth and no history of miscarriage. Consent was obtained from the respondents before data collection.

Interviewer-based structured questionnaires were administered in privacy. Serial numbers were assigned to each subject in both groups to protect their identity. The participants had fasting blood glucose (FBG) and fasting insulin levels (FI) assayed for after a 12-h fast. Based on these tests, the β-cell function and HOMA-IR (homeostasis model assessment of insulin resistance) index were computed using the HOMA-2 computer model. The information obtained included age, parity, gestational age, weight, height, body mass index (BMI), and number of consecutive miscarriages.

Laboratory tests

For the purpose of this study, fasting blood glucose and fasting insulin were assayed and β-cell function and HOMA-IR were computed. β-Cell dysfunction was defined as β-cell function less than the 25th percentile [18]. Abnormal glucose metabolism was defined as FBG ≥ 5.1 mmol/L [16]. Fasting blood glucose was analysed by automated colorimetric enzymatic analysis using commercial kits on the COBAS c111 automatic analyser (COBAS Roche Diagnostic, D-68305 Mannheim, Germany and DRG Diagnostics). Fasting insulin was assayed by BIOS Human insulin ELISA kits (Chemux Bioscience, Inc. USA). The assays were done according to the kit manufacturer's specifications.

Quality control

Analytical accuracy and precision was assured by simultaneous analysis of pooled serum quality control specimen with each batch of samples. The auto-analyser was calibrated and the routine maintenance was done in line with the manufacturer's specifications. The inter-batch coefficient of variance (CV) for glucose and insulin was 1.0%. The intra- and inter-batch CV for insulin were 1.9% and 9.0%, respectively, and these are within recommended limits.

Data analysis

The primary outcome measures were β-cell function and FBG levels in both groups. The secondary outcome measures were the FI and HOMA-IR. All statistical analyses were performed using SPSS software version 22.0 (IBM, Armonk, NY, USA). Frequencies and percentages were computed for demographic characteristics of both groups. Student's t test and Fisher's exact test were used to test the difference between groups which were appropriate. A P value of < 0.05 was considered as statistically significant at confidence interval (Cl) of 95%.

Results

This study consisted of 160 participants; 80 women with recurrent first trimester miscarriages and 80 women with first trimester normal pregnancy (comparison group). As shown in Table 1, no significant differences were observed between the two groups in terms of mean age, gestational age and BMI.

Table 2 shows a statistically significant higher prevalence of β-cell dysfunction among non-diabetic women with recurrent first trimester miscarriages compared to women with normal first trimester pregnancies (38.8% vs 10.0% respectively, $P < 0.001$). Also, the prevalence of abnormal glucose metabolism was higher among non-diabetic women with recurrent miscarriages compared to age-matched non-diabetic women with no history of miscarriages (27.5% vs 6.3%, $p = 0.005$).

Table 1 Clinical characteristics of the study participants

Characteristics	Recurrent miscarriage $N=80$ (%)	Normal pregnancy $N=80$ (%)	*P* value
Age (years)			
Mean ± SD	28.09 ± 6.14	28.10 ± 6.21	0.990
Parity			
Median (range)	1 (4)	1 (5)	
GA (weeks)			
Mean ± SD	10.68 ± 1.52	11.19 ± 1.87	0.066
No. miscarriages			
Median (range)	2 (4)	0 (0)	
BMI (Kg M^{-2})	25.25 ± 4.17	25.20 ± 4.13	0.930
Total	80 (100)	80 (100)	

Table 3 Comparison of mean values of fasting insulin, fasting blood glucose, HOMA-index, and beta cell function among women with recurrent miscarriages and normal pregnant women

Characteristic	Recurrent miscarriage	Normal pregnancy	*P* value
Insulin (mIU/L)	26.62 ± 14.62	25.15 ± 13.61	0.509
FBG (mmol/L)	4.77 ± 1.14	3.58 ± 0.78	< 0.001†
β-Cell funct.*	264.41 ± 105.13	447.82 ± 181.24	< 0.001†
Secretion (%)	58.97 ± 49.69	68.23 ± 78.67	0.375
HOMA-IR	3.76 ± 2.13	3.20 ± 1.79	0.074

HOMA-IR homeostasis of model assessment of insulin resistance index

β-cell funct.*–beta-cell function

†Significant

In Table 3 fasting glucose was significantly higher among women with recurrent miscarriages compared to the women with normal pregnancy (4.77 ± 1.14 mmol/L versus 3.58 ± 0.78 mmol/L, $P < 0.001$) and β-cell function was significantly lower in women with recurrent miscarriages than the age-matched normal group (264.41 ± 105.13 versus 447.82 ± 181.24, $P < 0.001$). There were no significant differences between fasting insulin (FI) and HOMA-IR of women with recurrent miscarriages and the normal group (26.62 ± 14.62 mIU/L versus 25.15 ± 13.61 mIU/L, $P = 0.509$) and (3.76 ± 2.13 versus 3.20 ± 1.79, = 0.074), respectively.

Table 4 shows that women with miscarriages were more likely to have low beta-cell function ($P < 0.001$) and elevated fasting serum glucose (≥ 5.1 mmol/L, $P < 0.001$). This significant association remained after controlling for gestational age, insulin resistance, impaired beta-cell function, and fasting serum glucose ≥ 5.1 mmol/L in a logistic regression analysis.

Discussion

The management of recurrent miscarriages remains a major challenge to gynaecologists. Impaired β-cell function and dysfunctional glucose metabolism may have a role to play in the occurrence of recurrent miscarriages in non-diabetics.

A statistically significant higher prevalence of β-cell dysfunction was observed among non-diabetic women with recurrent first trimester miscarriages compared to women with normal first trimester pregnancies. The mean β-cell function in the women with recurrent miscarriages was only 59.0% of the women with normal pregnancies. This observation was different from the report of Wang et al. in which a statistically insignificant lower prevalence was recorded in the miscarriage group among Chinese women [19]. The disparity in these observations may be due to differences in gestational age cut-off used in the two studies. Another possible explanation for the observed difference may be different genetic and metabolic profile that varies across populations.

The prevalence of abnormal glucose metabolism was higher among non-diabetic women with recurrent

Table 2 Prevalence of beta-cell dysfunction and abnormal glucose metabolism among women with recurrent miscarriage and normal pregnant women

Characteristic	Recurrent Miscarriage $n=80$ (%)	Normal pregnancy $n=80$ (%)	Total $n=160$ (%)	(*P* value) *
FBG ≥ 5.1 mmol/L**				
Yes	27 (33.8)	3 (3.8)	30 (18.8)	< 0.001
No	53 (66.2)	77 (96.2)	130 (81.2)	
Low β-cell function***				
Yes	31 (38.8)	8 (10.0)	39 (24.4)	< 0.001
No	49 (61.2)	72 (90.0)	121 (75.6)	

*Fisher's derived *P* value

**Fasting glucose diagnostic criteria for GDM [16]

***Low β-cell function—women with β-cell function less than the 25th percentile

Table 4 Bivariate and multivariate analysis of association between miscarriage and insulin resistance, FPG ≥ 5.1 mmol/L and low beta-cell function

Characteristic	Recurrent miscarriage $n=80$ (%)	Normal pregnancy $n=80$ (%)	Total $n=160$ (%)	X^2 (P value)*	Adjusted (P value****)
FBG ≥ 5.1 mmol/L**					
Yes	27 (33.8)	3 (3.8)	27 (16.9)	< 0.001	0.005†
No	53 (66.2)	77 (96.2)	133 (83.1)		
Low beta-cell function***					
Yes	31 (38.8)	8 (10.0)	39 (24.4)	< 0.001	0.001†
No	49 (61.2)	72 (90.0)	121 (75.6)		

FBG fasting blood glucose

*Fisher's derived *P* value

** Fasting glucose diagnostic criteria for GDM [16]

Low β-cell function***—women with β-cell function less than the 25th percentile

Adjusted *P* value****—adjusted for gestational age, insulin resistance, impaired β-cell function, and FBG ≥ 5.1 mmol/L

†Significant

miscarriages compared to the women with normal pregnancies. The mean FBG was statistically significantly higher among non-diabetic women with recurrent miscarriages compared to the women with normal pregnancies. These findings are consistent with the report of Wani et al. [20]. This was however not the case in other studies in which statistically significant differences were not noted between women with recurrent miscarriage and those with normal pregnancies [12, 17, 21]. This may be due to the fact that the women were recruited at higher gestational ages (20–24 weeks) in these studies. With increasing gestation the metabolic role of anti-insulin hormones increases which may neutralise the possible differences.

Another important observation in this study is the statistically significant association between recurrent miscarriages and fasting blood glucose (FBG) of ≥ 5.1 mmol/L and impaired β-cell function. This significant association remained after controlling for gestational age (GA), insulin resistance, impaired β-cell function, and fasting serum glucose ≥ 5.1 mmol/L in a logistic regression analysis (adjusted *P* values of 0.005 and 0.001 for FG ≥ 5.1 mmol/L and low β-cell function, respectively). Wang et al. did not find a statistical difference between the β-cell function of the patients and controls in their work [19]. It is worth noting that insulin resistance was not significantly associated with miscarriage in this study. Both groups had considerably high levels of HOMA-IR. The high level of HOMA-IR in women with normal first trimester pregnancy may be due to the counter regulatory effects of anti-insulin hormones (progesterone, oestrogens, cortisol, human placenta lactogen, and growth hormone).

It is important to note that a FBG ≥ 5.1 mmol/L is suggestive of a diagnosis of gestational diabetes mellitus [16]. In this study, 33.8% of the women with recurrent miscarriages had FBG ≥ 5.1 mmol/L. This means that a large percentage of the women with recurrent miscarriage had some level of deranged glucose metabolism. Therefore it is important for glycaemic status to be assessed early in pregnancy and women presenting with recurrent miscarriage should be evaluated to rule out abnormal glucose metabolism.

Conclusion

Our study suggests that non-diabetic women presenting with recurrent first trimester miscarriages should be evaluated to rule out deranged β-cell function and abnormal glucose metabolism. Also, glycaemic status should be assessed early in pregnancy especially in women with recurrent miscarriages and women with impaired β-cell function should be followed up with periodic oral glucose tolerance test (OGTT) for early diagnosis of gestational diabetes mellitus (GDM) and type 2 diabetes mellitus.

Limitations

This is a hospital-based study, therefore the findings may not reflect the findings in the general population of women with recurrent first trimester miscarriages. Also, genetic causes of first trimester miscarriages could not be excluded. Nutrition habits were not assessed and waist to hip score was not measured.

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Author contributions AEE: Conceptualization, original manuscript writing, data collection, data analysis/interpretation, and funding. UAA: Conceptualization, data collection, editing and proof reading. BJ: Manuscript review and editing. COE: Manuscript review and editing. CLI: Methodology, laboratory analysis, and interpretation of analysed data. OJ: Data collection. ASA: Supervision and editing. MS: Writing review and editing. All authors commented on previous versions of the manuscript, read, and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval Ethical approvals were obtained from the Research and Ethical Committees of the Jos University Teaching Hospital, Plateau State Specialist Hospital, and Fertile Ground Hospital.

Informed consent Written informed consent was obtained from the patient for publication.

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