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Original Article

The Comparison of Insulin Resistance Between Women with Recurrent Miscarriages and Normal Women in Jos, Nigeria

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ABSTRACT

Background: Insulin resistance (IR) has been implicated as an aetiological factor in recurrent first trimester miscarriages (RM), however, there are insufficient and conflicting evidence regarding its contribution to the occurrence of RM. ***Objective:*** This study aimed to investigate the association between insulin resistance and recurrent first- trimester miscarriages in comparison with first-trimester normal pregnancies. ***Design:*** Comparative cross-sectional study. **Methodology**: This study involved 80 women with history of RM and 80 women with first-trimester pregnancies with at least one live birth and no history of miscarriage (control group). Interviewer-administered questionnaires were used to obtain relevant information including age, gravidity, parity, gestational age and number of consecutive miscarriages. From each participant fasting blood glucose and fasting insulin were assayed by automated colorimetric enzymatic analysis and BIOS Human insulin ELISA kits respectively. ***Statistical Analysis:*** Data was analysed using IBM SPSS version 22.0. **Results:** Prevalence of IR in case and control groups were 48.8% and 27.5% respectively. Insulin resistance was significantly higher in cases compared to the controls. Fasting blood glucose was significantly higher in women with RM than in the control group. There was no significant difference between fasting insulin of women with RM and controls. **Conclusion:** This study suggests that women with recurrent first-trimester miscarriages are more likely to have underlying insulin resistance with higher fasting blood glucose levels compared to women with normal first trimester pregnancies.

Keywords: Recurrent first-trimester miscarriages, Insulin resistance, Jos-Nigeria

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Introduction

Effective Management of couples with recurrent miscarriages remains a mirage until the cause is known and addressed. In about 50% of women with recurrent miscarriages the cause(s) is/are not known, hence the need for further research.[1] Recurrent miscarriages (RM) affect 2-4% of reproductive age couples, representing a challenge for the attending clinicians.[2] It affects both naturally conceived pregnancies and those obtained after assisted reproductive technology treatment.[3]

Multiple factors have been ascribed to RM aetiology, these include chromosomal anomalies, genetic, hormonal, anatomic, systemic, immunologic, infectious and endocrine but 50% of cases remain unexplained.[1,4] Endocrine disorders like poorly controlled diabetes, polycystic ovary disease (PCOD), hyperandrogenism, luteal phase defect and thyroid disorders have been frequently linked to recurrent pregnancy loss because embryo attachment and early implantation are controlled by local hormonal milieu causing endocrine-related pregnancy failure.[5]

Insulin resistance (IR), hyperinsulinaemia and hyperandrogenaemia in PCOD have been linked with metabolic and endocrine abnormalities associated with recurrent miscarriages.[4,6] Recent studies showed that insulin resistance could be a cause, independent of PCOD status.[2,3,7] Therefore, insulin resistance might be one of the direct causes of recurrent miscarriages in non-PCOD affected women.[1,8,9]

Insulin resistance increases plasminogen activator inhibitor-1 (PAI-1) expression;[3,10] an endogenous inhibitor of fibrinolysis.[2,11] PAI-1 increases serum insulin and it induces a hypofibrinolytic state.[10,12] This creates a thrombotic milieu at the maternal-foetal interface with a high risk of miscarriage.[11,13,14] Insulin resistance predisposes to ovarian androgen excess and may promote miscarriage by increasing circulating androgen concentration.[2,15]

Hyperinsulinemia has been shown to decrease the expression of glycodelin and insulin like growth factor binding protein-1 (IGFBP-1) at the implantation site.[3,16] Glycodelin plays an important role in inhibiting the endometrial response towards the embryo, while IGFBP-1 facilitates the adhesion process of the blastocyst at the foeto-maternal interface.[17,18] Studies have also suggested that insulin resistance and/or hyperinsulinemia may cause homocysteinemia;[5,18] which may impair pregnancy by interfering with endometrial blood flow and vascular integrity.[12] It increases the oxidative stress in vascular endothelium, activates platelet and has been documented to increase the probability of early pregnancy loss.[4,19] The polycystic ovary syndrome like status, due to elevated fasting insulin (FI) and high IR, and the successful use of metformin for the treatment of PCO suggested the idea that metformin could be used in these women.[4,20,21]

Insulin resistance is one of the remediable factors that may be a direct cause of RM. There are however, insufficient and conflicting evidence (association and no association) to infer this conclusion. This study was done to understand the association between insulin resistance and recurrent miscarriages in non-PCOS affected women in order to contribute to the existing body of knowledge and effective prevention.

Materials and Methods

This comparative cross-sectional study was conducted at the Jos University Teaching Hospital (JUTH), Plateau State Specialist Hospital (PSSH) and Fertile Ground Hospital (FGH), all of which are in the cosmopolitan city of Jos, Plateau State, Nigeria.

The study population comprised eligible women with history of recurrent first trimester miscarriages seen between August 2016 and January 2018 (18 months). Pregnancy loss was defined based on ultrasound documentation of intrauterine gestation or presence of normal trophoblastic tissues on histopathological examination of evacuated specimen. First trimester pregnancy loss was defined as any spontaneous miscarriage occurring on or before 13 weeks of gestation. Gestational age was determined by ultrasound dating.

Women with at least 2 consecutive first trimester miscarriages were recruited into the case group, while the control group comprised women within the same age range (±1 year) with at least one live birth and no history of miscarriage. Cases and controls were recruited by consecutive sampling technique. Women who refused consent and women with pregnancy losses attributable to known causes or on treatment for a known cause including diabetics, ectopic and molar gestations, and PCOD were excluded. PCOS status was determined based on at least 2 of the revised Rotterdam criteria: Oligo- and/or anovulation, hyperandrogenism and polycystic ovaries with exclusion of other aetiologies.

Ethical clearances were obtained from the Research and Ethical Committees Boards of the three participating hospitals.

Structured questionnaires were interviewer-administered in privacy. Serial numbers were assigned to all participants for anonymity. The subjects were asked to go on their usual diets for at least 3 days then fasted for 12 hours and blood was drawn. The information obtained included; age, gravidity, parity, gestational age, levels of education, occupation and number of consecutive miscarriages. Body mass index was calculated from weight and height.

Laboratory Tests

Fasting blood glucose and fasting insulin were assayed and HOMA-IR computed. Insulin resistance (IR) was defined as HOMA-IR >4.5[2,3,11,14] 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).

Calculation of Results

A calibration curve was plotted using absorbance obtained from each standard against its concentration. The absorbance value was plotted on the vertical (Y) axis and concentration on the horizontal (X) axis. The corresponding concentration of the sample was obtained from the calibration curve.

Quality Control

Serum specimens were pooled together and analysed simultaneously to ensure quality control. The auto-analyser was calibrated and routine maintenance was done in line with manufacturer 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% and these are within recommended limits.All samples were analysed in the same laboratory, using same test kits and by same scientist to eliminate intra and inter observer errors.

Estimation of Sample Size

The sample size was estimated using the formula;

$$n = \frac{\{P1\,(1-P1) + P^2\,(1-P2)\}X\,(Z\acute{a} + Z\hat{a})^2}{(P1-P2)^2}$$

Where: n: number of sample size in each of the group.

P1= proportion of insulin resistance among cases (0.24 in a similar study).[11]

P2= proportion of insulin resistance among controls (0.08 in the same study).[11]

Z-á/2= value of standard normal distribution corresponding to a significance level of alpha (1.96 for two-sided test at the 0.05)

Z-â/2=value of standard normal distribution corresponding to the desired level of power (0.84 for a power of 80%)

$$n = \frac{\{(0.24\times0.76 + 0.08\times0.92)\}x\,(1.96 + 0.84)^2}{(0.16)^2} = 78$$

The sample size was adjusted to 80 for the cases and 80 for the controls to compensate for an attrition rate of 2.5%.

Data Analysis

All statistical analyses were performed using IBM SPSS software version 22.0. Frequencies and percentages were computed for demographic characteristics of the cases and comparison group.

Student's t-test, Chi square test and Fisher's exact test were used to test the difference between groups where appropriate. A p-value of <0.05 was considered as statistically significant at confidence interval (Cl) of 95%.

Results

This study consisted of 80 cases and 80 controls. The RM and control groups were comparable in terms of maternal age, gestational ages and body mass index. The mean age of women with RM was 28.09±6.14 years and that of the control group was 28.10±6.21 years. The mean gestational ages of the study participants in both groups were approximately 11 weeks. The mean BMI of RM and control groups were in the overweight category (=25=29.9 Kgm-2). Sixty percent of the study population had tertiary education, 2.5% had no formal education and 30.0% were housewives. There were no significant differences with respect to levels of education and occupation between the RM and control groups, P > 0.05. This clinical characteristics of the study participants have been reported in an earlier publication.[22]

Table 2, shows the mean concentrations of fasting blood glucose (FBG) and fasting insulin (FI) and prevalence of HOMA-IR for both cases and controls. The prevalence of insulin resistance was higher among women with recurrent miscarriages than women with normal pregnancies, 48.8% versus 27.5% and this was statistically significant, P=0.009.There was a statistically significant difference between the mean fasting blood glucose of cases and comparison group, P <0.001. No statistically significant difference was observed in the fasting insulin concentrations of both groups, even though it was relatively higher among women with recurrent miscarriages.

Fasting blood glucose, fasting insulin and insulin resistance were observed to be higher in women with at least 3 successive miscarriages compared to 2 consecutive miscarriages but these relative increases were not statistically significant.

Table 1: Clinical characteristics of the study participants.[22]

Characteristics	Recurrent miscarriage N = 80(%)	Normal pregnancy N = 80(%)	Total N = 160(%)	P-Value
Age (years)				
Mean ± SD	28.09 ± 6.14	28.10 ± 6.21	28.10±6.18	0.990
Gravidity				
Median (range)	3 (6)	2 (5)		
Parity				
Median (range)	1 (4)	1 (5)		
No. of miscarriages				
Median (range)	2 (4)	0 (0)		
GA (Weeks)				
Mean ± SD	10.68 ± 1.52	11.19 ± 1.87	10.94±1.70	0.066
BMI (Kg/m^2)	25.25 ± 4.17	25.20 ± 4.13	25.23±4.15	0.930
Education				
Informal	4(5.0)	0(0.0)	4(2.5)	
Primary	5(6.3)	4(5.0)	9(5.6)	0.164**
Secondary	22(27.5)	29(36.3)	51(31.9)	
Tertiary	49(61.2)	47(58.7)	96(60.0)	
Occupation				
House wife	21(26.3)	27(33.8)	48(30.0)	
Self-employed	25(31.2)	25(31.2)	50(31.3)	
Student	8(10.0)	9(11.3)	17(10.6)	0.789**
Teaching	6(7.5)	3(3.7)	9(5.6)	
Banking	2(2.5)	1(1.3)	3(1.9)	
Civil servant	18(22.5)	15(18.7)	33(20.6)	
Total	**80(100)**	**80(100)**	**160(100)**	

* Chi-Square test derived value
** Fishers exact test derived value

Table 2: Comparison of mean values of Biochemical data, Prevalence of Insulin Resistance and Test of association between insulin resistance and recurrent miscarriages in cases and comparison group.

Characteristics	Recurrent miscarriage N = 80(%)	Normal pregnancy N = 80(%)	Total Average N = 160(%)	P-Value
FBG (pmol/L)				
Mean±SD	33.13±7.92	24.86±5.42	29.03±6.67	<0.001†
FI(mIU/L)				
Mean±SD	26.62±14.62	25.15±13.61	25.89±14.12	0.509
HOMA-IR				
>4.5	39(48.8)	22(27.5)	61(38.1)	0.009*
≥4.5	41(51.2)	58(72.5)	99(61.9)	

HOMA-IR - Homeostasis Model Assessment of Insulin Resistance index
6.945 ñmol/L = 1 mmol/L * Chi Square value † Significant

Table 3: Relationship between number of recurrent miscarriages and insulin resistance

Characteristics	Number of Recurrent miscarriage (RM): n = 80(%)		
	2 RM	≥ 3 RM	p- value
	n = 48 (60)	n = 32 (40)	
FBG (pmol/L)			
Mean ± SD	32.50±7.49	34.00±8.55	0.409
FI (mIU/L)			
Mean ± SD	25.12±14.47	28.88±14.79	0.262
Mean HOMA-IR			
Mean ± SD	3.52±2.10	4.12±2.15	0.216

Discussion

In this study HOMA-IR values above 4.5 identified all participants with possible insulin resistance.[2,3,14] Although there are no universally accepted reference values for classifying individuals as insulin resistant,[23] the 25 percentile of a given population with lowest insulin sensitivity or highest Insulin resistance are generally recommended .[24]

The prevalence of insulin resistance among women with recurrent first trimester miscarriages and women with normal first trimester pregnancies was 48.8% and 27.5% respectively. This observed difference with higher prevalence among cases was statistically significant. These results are comparable with the findings of Craig LB et al and Wani AA et al where prevalence of 21.6% and 24.0% in the case groups and 8.1% and 8.0% among control groups were reported respectively.[2,25] These differences were statistically significant with P-values of 0.003 and 0.04 respectively. The results of this study, are also consistent with the study of Tian et al among women who had assisted reproductive technology treatment for infertility.[3] Insulin resistance status was determined before treatment as HOMA-IR >4.5. Among women that had miscarriages following treatment 47.8% were insulin resistant against 9.5% of women who had no insulin resistance but later had miscarriage.[3] Li ZL et al found a significantly higher proportion of women with HOMA-IR >4.5 among women with recurrent miscarriages in a large systematic review and meta-analysis which included 7 studies conducted between 1996 and 2012 involving 467 women with recurrent miscarriages and 413 control.8. Diejomaoh et al got a prevalence, in Kuwait of 22.9% among women with history of recurrent spontaneous miscarriages of unknown aetiology and 6.7% among women with normal pregnancies.[14]

The higher prevalence of IR recorded in this study may be related to the use of same cut-off for insulin resistance across different populations, life styles and diets. Another probable explanation for the observed difference may be related to genetic and metabolic profiles that vary across populations.

In our study there was no statistical significant difference between the two groups with respect to age and BMI. These comparable data in both groups were because the patients and their controls were matched for age, weight and height as in other studies. Wani AA et al and Craig LB et al reported similar comparable mean ages in their studies; (28.40±2.37 vs 29.10±2.70) years and (32.70±5.40 vs 32.80±6.00) years respectively.[2,25] The mean body mass index reported in our study is similar to that of Craig LB et alwhere the mean BMI in their study and control groups were comparable (29.20±7.30kg/m2 vs 29.00±7.20kg/m2).2 These results were also consistent with the study of

Wani AA et al where the mean BMI in the study group was 23.90±2.15kg/m2 and in the control group was 23.5±2.07kg/m^2.[25]

The difference in mean gestational ages was not significant between the two groups. This is consistent with the results of Tamara et al in which mean gestational ages of 7.20±0.80 and 7.50±0.60 weeks were reported among cases and controls respectively.[26]

Mean fasting blood glucose was significantly higher in women with recurrent first trimester miscarriages than the comparison group. The results were consistent with the findings of the studies by Tian et al and Wani AA et al where mean fasting blood glucose in the study groups were 5.31±0.43mmol/L and 5.36±0.44mmol/L respectively and 4.98±0.57mmol/L and 4.84±0.64mmol/L in the control groups respectively.[3,25]

Insulin resistance was found to be significantly associated with recurrent first trimester miscarriages in this study. The mechanisms by which insulin resistance causes miscarriage is not clearly known. Therefore it is important for insulin resistance status to be assessed early in pregnancy and women presenting with recurrent miscarriages should be evaluated to rule out abnormal glucose metabolism and where necessary life style modification and or insulin sensitizer could be recommended. This was 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.

Conclusion

This study suggests that women with recurrent first trimester miscarriages are more likely to have underlying insulin resistance with higher fasting blood glucose levels compared to normal controls. Successful use of metformin to lower insulin resistance in women with PCOD might suggest the use of metformin for pre and peri-conception care in this group of women.[4,20,21] There is need to further investigate this to validate its inclusion as a routine test in the investigation of women with recurrent miscarriages.

- ***Ethical aspect (beneficence):*** They were counselled and educated on the results and its future implications, need for life style and dietary modification, need for regular glucose monitoring and then co-managed with the endocrinologist.

- ***Acknowledgment:*** We wish to acknowledge the residents in the department of Obstetrics and Gynaecology of Jos University Teaching Hospital, Plateau State Specialist Hospital and Fertile Ground hospital/IVF-ET centre for their contributions in the recruitment of the subjects for the study. We appreciate the Research and Ethical Committees for granting us approval for this study. We wish to say thank you to Mr Ajiji of Chemical Pathology department JUTH for helping with processing and storage of the samples.

- ***Conflict of interest:*** we declared that we have no conflict of interest

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