

Occurrence of Insulin Resistance with Recurrent Pregnancy Loss of Unknown Etiology in North Indian Hospital-based Women Population: A Pilot Study

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ABSTRACT

Objective: Recurrent pregnancy loss (RPL) has been defined as occurrence of two or more clinically recognized spontaneous consecutive pregnancy losses prior to the 20th gestational weeks according to new guidelines of the American Society of Reproductive Medicine. Although multiple factors have been explained for RPL but still in most of the cases no etiology is found.

Study design: It was a prospective analytical observational study. It was conducted on 100 nonpregnant women in reproductive age-group 20–30 years, 50 women, with history of two or more consecutive spontaneous abortions in study group and 50 women with at least one live birth and no history of recurrent abortions in control group. These two groups were matched for age and BMI. All the women underwent various examinations like ultrasound pelvis for ruling out any uterine anomaly, hysteroscopy, antiphospholipid profile, hormonal profile, screening for DM, and thyroid disorders, HOMA-IR was calculated for insulin resistance.

Result: A significant difference (<0.0001) was observed in fasting blood sugar and serum insulin levels in the case and control groups (<0.0005). HOMA-IR was also found to be significantly increased in RPL group ($p \leq 0.0005$).

Conclusion: Insulin resistance and hyperinsulinemia may be an important risk factor in women with idiopathic RPL.

Keywords: HOMA-IR, Insulin resistance, Pregnancy outcome, Recurrent pregnancy loss (RPL), Unexplained etiology.

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INTRODUCTION

Many human conceptions end in miscarriage and recurrent pregnancy (RPL) loss is a common complication of pregnancy. RPL is defined as loss of two or more consecutive and clinically recognized pregnancies before 20 weeks' gestation.¹ Most physicians recommend evaluation after two consecutive losses.² The American Society of Reproductive Medicine (ASRM) defines recurrent pregnancy loss as two or more pregnancy losses and recommends early investigation into the etiology after two losses as it is likely to result in continuation of pregnancy with fruitful conception.

The incidence of recurrent pregnancy loss is 2–5% of all couples in the reproductive age-group.³ Epidemiological studies have suggested that the disease might be multifactorial, with a possible genetic predisposition and involvement of environmental factors in its pathogenesis.⁴ Anatomic abnormalities contribute to 10–15% cases of RPL.⁵ Luteal phase defect (LPD), polycystic ovarian syndrome (PCOS), diabetes mellitus, thyroid disease, and hyperprolactinemia are the most common endocrinological disorders implicated in approximately 17–20% of RPL cases.⁶ Approximately 2–4% of RPL is associated with a parental balanced structural chromosome rearrangement.⁵ Other known causes of RPL include antiphospholipid antibodies (APA), and thrombophilias.⁷ Unfortunately, standard evaluation for cause of RPL typically leave one-half of patients with this disorder unexplained.⁷

Evaluation of certain population groups that have a higher incidence of idiopathic pregnancy loss have suggested other potential etiologies like hyperinsulinemia, insulin resistance, and increased plasminogen activator inhibitor activity for

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unexplained recurrent pregnancy loss. Insulin resistance is a condition in which cell receptors which are the target site for insulin action do not respond to the hormone insulin and resultant hyperinsulinemia.⁸ Insulin resistance is often associated with a hypercoagulable state (impaired fibrinolysis) and increased inflammatory cytokine levels.⁹

In view of this, we planned this study aiming to investigate the prevalence of IR and hyperinsulinemia in patients with RPL with unknown etiology.

MATERIALS AND METHODS

This was an observational, hospital-based, prospective analytical study conducted on 100 nonpregnant women in the reproductive age-group. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from all the patients. These women were divided into two groups, Group A (Study group), comprising 50 nonpregnant women in the age-group of 20–35 years with history of two or more consecutive spontaneous abortions of unexplained etiology. The exclusion criteria included ongoing pregnancy, obesity, Diabetes Mellitus, PCOS, Hypertension, and any other ongoing medical disorder. Group B (control group) fulfilled the same selection and exclusion criteria except that these women had at least one previous live baby, no history of recurrent spontaneous abortions, and no history suggestive of gestational D.M., for example, big-sized baby, hydramnios, etc.

The two groups were matched for age and BMI. All the women underwent following examinations, viz. ultrasonography, hysterosalpingography or hysteroscopy, serum thyroid profile, prolactin, LH/FSH ratio, APLA screening. The women with any known etiology were excluded. Sixteen women were excluded from the study group. The blood samples for fasting glucose and fasting insulin were collected after 12 hours fasting in plain tubes. Blood samples were centrifuged immediately after clot formation. The fasting glucose was determined soon after the separation of serum. Blood glucose was determined by GOD/POD method. For fasting insulin levels, serum was kept in aliquots at about -20°C (in deep freeze) and it was determined by ELISA.

We used the homeostasis model assessment of insulin resistance (HOMA-IR) index in both groups. $HOMA\ IR = \frac{FG\ (mg/dL) \times FI\ (IU/mL)}{405}$. Fasting insulin of >7.5 IU/mL was considered as hyperinsulinemia and a cut-off value of 1.5 for HOMA-IR being considered as diagnostic for insulin resistance.¹⁰

The results were analyzed by SPSS version 22. Continuous variables were presented as mean ± standard deviation. Value less than 0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

In this study, both the groups were matched for age and BMI. The mean age of women was 25.1 ± 3.0 years and 25.8 ± 2.8 years in case and control groups, respectively with no statistically significant difference ($p = 0.249$). The mean BMI in group A was 21.91 ± 1.98 and in group B was 21.47 ± 2.52 which is also statistically insignificant.

Fasting blood glucose was estimated in both the groups. The women in both groups were in euglycemic range with mean fasting blood sugar 83.82 ± 6.51 mg/dl in study group and 75.26 ± 7.43 mg/dl in control group, p value was statistically significant (<0.0001).

The mean fasting insulin was 10.13 ± 6.47 µIU/mL and 5.43 ± 3.45 µIU/mL in group A and group B, respectively. The difference was found to be statistically significant.

Mean HOMA-IR was 2.07 ± 1.27 in the study group and 1.02 ± 1.07 in the control group the difference was statistically significant (Tables 1 and 2).

DISCUSSION

In this study it was observed that both insulin resistance and hyperinsulinemia were significantly associated with recurrent

Table 1: Demographic profile of study and control groups

Parameters	Study group (Group A)	Control group (Group B)	p-value
	Mean ± SD	Mean ± SD	
Age (years)	25.1 ± 3.0 years	25.8 ± 2.8 years	0.249
Pregnancy loss	2.74 ± 0.98	0.1 ± 0.2	<0.0001
BMI	21.91 ± 1.98	21.47 ± 2.52	0.334
Fasting glucose (mg/dl)	83.82 ± 7.51	75.26 ± 6.43	<0.0001
Fasting insulin (IU/mL)	10.13 ± 6.47	5.73 ± 3.45	<0.0005
HOMA-IR	2.07 ± 1.27	1.02 ± 1.07	<0.0005

Table 2: Comparison of insulin resistance in two groups based on fasting insulin levels and HOMA IR

Fasting insulin (IU/mL)	Cases (34)		Control (50)	
	No.	%	No.	%
>7.5	21	61.8%	6	12%
<7.5	13	38.2%	44	88%
HOMA-IR				
>1.5	22	64.7%	6	12%
<1.5	12	35.3%	44	88%

pregnancy loss. It appears to be similar to the insulin status of the women with polycystic ovarian syndrome.

Hyperinsulinemia adversely affects the preimplantation environment by decreasing the expression of glycodelin and IGF-binding protein-1¹¹ which may play a role in inhibiting the endometrial immune response of the embryo, and seems to facilitate adhesion processes at the fetomaternal interface.

In our study, there was a statistically significant difference in the fasting glucose levels (83.82 ± 7.51 mg/dL, 75.26 ± 6.43 mg/dL) and fasting serum insulin levels (10.13 ± 6.4 µIU/mL, 5.73 ± 3.45 µIU/mL) in case vs control groups. Similar findings have been reported by Wani et al.,¹² Celik Nazan et al.,¹³ KA Wahba et al.,¹⁴ and Wang Y Zhao et al.¹⁵ The HOMA- IR value in our study was 2.07 ± 1.27 in the cases group and 1.02 ± 1.07 in control group which is in congruence with the findings of the study done by Corrina-Alina et al.¹⁶ where mean HOMA- IR in the study group was 2.98 and in the control group was 1.69 with a significant p value <0.001.

CONCLUSION

It is concluded that Insulin resistance is associated with RPL with unexplained etiology when fasting blood glucose, fasting insulin and HOMA-IR are used to measure insulin resistance. More studies are needed to explore the mechanism of insulin resistance in pregnancy loss.

REFERENCES

- Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril* 2013;99(1):63. DOI: 10.1016/j.fertnstert.2012.09.023
- Grattan D, Ladyman S. Hormonal induction of leptin resistance during pregnancy. *Physiol Behav* 2007;91(4):366–374. DOI: 10.1016/j.physbeh.2007.04.005



3. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril* 2012;98(5):1103–1111. DOI: 10.1016/j.fertnstert.2012.06.048
4. Jeddi-Tehrani M, Torabi R, Mohammadzadeh A, et al. Investigating association of three polymorphisms of coagulation factor XIII and recurrent pregnancy loss. *Am J Reprod Immunol* 2010;64(3):212–217. DOI: 10.1111/j.1600-0897.2010.00838.x
5. Ford BH, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. *Rev Obstet Gynecol* 2009;2(2):76–88.
6. Mtiraoui N, Borgi L, Hizem S, et al. Prevalence of antiphospholipid antibodies, factor V G1691A (Leiden) and prothrombin G20210A mutations in early and late recurrent pregnancy loss. *Eur J Obstet Gynecol Reprod Biol* 2005;119(2):164–170. DOI:10.1016/j.ejogrb.2004.07.00
7. Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. *Fertil Steril* 1996;66(1):24–29.
8. Jakubowicz DJ, Essah PA. Reduced serum glycodelin and insulin like growth factor binding protein-1 in women with polycystic ovary syndrome during first trimester of pregnancy. *J Clin Endocrinol Metab* 2004;89(2):833–839. DOI: 10.1210/jc.2003-030975
9. Craig LB, Ke RW, Kutteh WH. Increased prevalence of insulin resistance in women with a history of recurrent pregnancy loss. *Fertil Steril* 2002;78(3):487–490. DOI: 10.1016/s0015-0282(02)03247-8
10. Kulshreshtha B, Ganie MA, Praveen EP, et al. Insulin response to oral glucose in healthy, lean young women and patients with polycystic ovary syndrome. *Gynecol Endocrinol* 2008;24(11):637–643. DOI: 10.1080/09513590802342858
11. Giudice LC. Endometrium in PCOS: Implantation and predisposition to endocrine CA. *Best Pract Res Clin Endocrinol Metab* 2006;20(2): 235–244. DOI: 10.1016/j.beem.2006.03.005
12. Wani AA, Gul I, Jabeen F, et al. Relationship of insulin resistance with recurrent pregnancy loss. *Int J Reprod Contracept Obstet Gynecol* 2017;6(4):1312–1317. DOI: 10.18203/2320-1770.ijrcog20171384
13. Nazan C, Evsen MS, Sak ME, et al. Evaluation of the relationship between insulin resistance and recurrent pregnancy loss. *Ginekol Pol* 2011;82(4):272–275.
14. Wahba KA. Assessment of the role of insulin resistance in cases of recurrent unexplained first trimesteric miscarriage. *Life Sci J* 2015;12(7):174–181.
15. Wang Y, Zhao H, Li Y, et al. Relationship between recurrent miscarriage and insulin resistance. *Gynecol Obstet Invest* 2011;72(4):245–251. DOI: 10.1159/000325165
16. Ispasoiu CA, Chicea R, Stamatian FV, et al. High fasting insulin levels and insulin resistance may be linked to idiopathic RPL. *Int J Endocrinol* 2013;2013:576926. DOI: 10.1155/2013/576926