Assessment of the Role of Insulin Resistance in Cases of Recurrent Unexplained First Trimesteric Miscarriage

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Abstract: Objective: To assess the role of insulin resistance in cases of recurrent unexplained 1st trimesteric miscarriage and to show whether investigations for insulin resistance should be added to the routine investigations of recurrent miscarriage or not. **Design**: A prospective case control study. **Setting:** The recurrent miscarriage clinic in a tertiary center (Ain Shams University Maternity hospitals). **Population:** Cases were 180 non-pregnant women with recurrent primary or secondary unexplained 1st trimestric miscarriage (≥ 3 consecutive 1st trimestric miscarriages). Controls were 180 non-pregnant women that matched the cases regarding their age, BMI and had a completely normal obstetric history. **Methods:** All cases and controls had full assessment regarding their history and examination. Investigations for fasting blood glucose, fasting insulin and full lipid profile were undertaken for all. **Outcomes:** Primary outcome included fasting insulin levels. Secondary outcomes included fasting blood glucose, fasting glucose-insulin ratio and HOMA calculator results (including insulin resistance, B-cell function and insulin sensitivity). Abdominal girth at the umbilicus, positive family history of D.M., abnormal lipid profile and previous history of macrosomia were also considered. **Results:** No significant difference in age, BMI and abdominal girth were found between cases and controls. The mean fasting blood glucose, fasting insulin, HOMA insulin resistance & HOMA B cell function was significantly higher in cases in comparison to controls. The HOMA insulin sensitivity was significantly lower in cases in comparison to controls. 26.11% of cases had fasting glucose – insulin ratio <4.5 in comparison to 11.67% of controls and this was highly significant. **Conclusion:** Frequency of insulin resistance is significantly high in cases with recurrent unexplained 1st trimestric miscarriage. Insulin resistance may probably be an important cofactor for causing recurrent pregnancy loss. **Recommendations:** A further study will be done on the cases in this study to assess the effect of Metformin intake during pregnancy to improve the pregnancy outcome.
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Keywords: insulin resistance, fasting glucose, fasting insulin, recurrent miscarriage.

1. Introduction:

Miscarriage involves approximately 15% of pregnancies. Recurrent miscarriage (i.e ≥ 3 spontaneous miscarriages) is a rather rare condition with an estimated incidence of 1% to 3%. A multidisciplinary approach in the evaluation of miscarriage is essential to understand the cause and risk of recurrence [1].

Known risk factors for recurrent miscarriage are genetic and endocrinal disorders, uterine pathology, nutritional and environmental factors, infections, alloimmune and autoimmune diseases, and thrombophilias [2]. However, despite years of investigations, the etiology is not established in up to 50% of cases [1].

Recurrent miscarriage remains a very disturbing event to the affected patients by this health problem; they are always anxious to find the underlying reasons for their miscarriages. This is also a major challenge to the treating physicians [3].

In couples with recurrent miscarriage, chromosomal abnormalities of the embryo account for 30-57% of further miscarriages [4, 5] whereas antiphospholipid syndrome is the most important treatable cause of recurrent miscarriage [6].

Women with diabetes who have high haemoglobin A1c levels in the first trimester are at higher risk of miscarriage and fetal malformations [7]. Women with Polycystic ovarian syndrome (PCO) are as well at higher risk of miscarriage and this may be attributed partly to the insulin resistance in such patients [8].

A number of studies document a possible association between insulin resistance and hyperhomocysteinemia which may lead to premature vascular disease and early damage to decidual or chorionic vessels and eventually cause miscarriage in PCO patients [9-11].

The mechanisms responsible for insulin resistance include genetic or primary target cell defects, autoantibodies to insulin, accelerated insulin degradation or mitochondrial cell dysfunction. Obesity is associated with a decreased number of insulin receptors together with a post-receptor failure to activate tyrosine kinase [12, 13].

The syndrome of insulin resistance actually make up a broad clinical spectrum which includes obesity,

glucose intolerance, diabetes, the metabolic syndrome as well as an extreme insulin resistant state [14].

In clinical practice, no single laboratory test is used to diagnose insulin resistance. Diagnosis is based on clinical findings corroborated with laboratory tests. Some laboratory tests are accurate but difficult to perform as the euglycemic insulin clamp technique. Others are much easier to be performed but less accurate as fasting blood glucose level, fasting insulin level, fasting glucose-insulin ratio, homeostatic model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). Some other laboratory investigations are also helpful as a full lipid profile, homocysteine level, plasminogen activator inhibitor-1 level and electrolyte levels [15].

The role of insulin resistance as a possible cause of recurrent unexplained miscarriage is still controversial as most of the studies in the literature were on small numbers of patients and many studies were on patients with PCO.

In this study we are going to assess the role of insulin resistance in recurrent unexplained 1st trimesteric miscarriage and whether investigations for insulin resistance should be added to the routine investigations of recurrent miscarriage or not.

2. Patients and Methods

This was a prospective case control study conducted in Ain Shams University Maternity hospitals between August 2012 and August 2013. The study was conducted after approval of the hospital ethical committee according to the World Medical Association Declaration of Helsinki and a written consent was taken from all cases and controls participating in the study after full explanation. The cases (n=180) were non pregnant patients attending the recurrent miscarriage clinic during that period as old or new patients. All the cases had an age between 18 and 40 years. They had either primary or secondary recurrent first trimesteric miscarriage (i.e $\geq$ 3 consecutive miscarriages with (2 ry) or without (1 ry) previous deliveries.

All of them underwent routine investigations for recurrent miscarriage and they were all normal. These routine investigations included cytogenetic study of the products of conception (at least once before) together with karyotyping for the couple, investigations for PCO, trans-vaginal ultrasound, thyroid functions including anti-thyroid antibodies, screening for diabetes, antiphospholipid antibodies, investigations for congenital and acquired thrombophylias.

The controls (n = 180) were non pregnant patients matched to cases as regards to age and BMI. They had a completely normal obstetric history with no previous miscarriages. They were all medically free. They were attending other clinics for consultation (as the gynecology or family planning clinic).

Both cases and controls had full assessment regarding their history (with special concentration on the obstetric history, family history of diabetes, consanguinity and past medical history). Height, weight, BMI and abdominal girth at the umbilicus were measured for all cases & controls.

Blood was withdrawn from the cases and controls for the determination of the fasting blood glucose and fasting insulin levels (by the radioimmunoassay technique) together with a full lipid profile.

All cases and controls had an overnight fast of 10 hours before blood was extracted. The Homeostatic model assessment 2 (HOMA 2) calculator was used to detect the insulin sensitivity, B cell function and insulin resistance. The fasting glucose – insulin ratio was also calculated.

Statistical Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Continuous variables are expressed as mean and standard deviation. Categorical variables are expressed as frequencies and percents. Student test was used to compare quantitative variables between both groups. Chi-square test was used to compare qualitative variables between both groups. Pearson's correlation coefficient was used to calculate correlation between paired data sets.

The ROC curve & AUC were used to show the prediction of the laboratory test for the problem (recurrent miscarriage). Statistical significance was considered present if the P-value was less than 0.05.

3. Results:

A total of 51.7% (n=93) of cases suffered from 1ry miscarriage and 48.3% (n=87) suffered from 2ry miscarriage. The number of miscarriages ranged from (3-10) with the highest frequency of 3 (55.6%) (n=100) followed by 4 (23.3%) (n=42) then 5 (12.2%) (n=22).

The number of deliveries in the control group ranged from (1-6) with the maximum frequency of 2 deliveries 45.56% (n=82) followed by 1 delivery 21.67% (n=39) followed by 3 deliveries 18.89% (n=34).

Both cases & controls were matched for age, weight, height, BMI and abdominal girth at the umbilicus with no significant difference between both groups. There was a significantly higher mean fasting blood glucose, higher mean fasting blood insulin, higher mean insulin resistance, higher mean B-cell function in case compared to controls. The fasting glucose – insulin ratio was lower in cases in

comparison to control with no significant difference. Insulin sensitivity was lower in cases in comparison to controls but with no significant difference (Table 1). 26.11% (n = 47) of cases had fasting glucose- insulin ratio <4.5 in comparison to 11.67% (n = 21) of controls with high significant difference.

Table 1:Comparing the demographic data and investigations of insulin resistance between cases and controls

	Cases Mean ± S.D (range)		Controls Mean ± S.D (range)		t-test	*P*
Age (yrs)	30.36±5.3 (18-40)		30.43±5.5 (18-41)		-0.127	>0.05
*Wt(kg)	71.48±12.6 (49-113)		71.93±12.8 (52-113)		-0.336	> 0.05
*Ht(cm)	163.79±4.6 (151-178)		164.67±4.5 (154-176)		-1.838	>0.05
BMI	26.59±4.2 (19.8-39)		26.55±4.8 (19.3-42)		0.082	>0.05
Abdominal girth(cm)	91.72±11.2 (69-123)		89.47±11.2 (70.5-128)		1.908	>0.05
*FBS (mg/dl)	86.76±9.8 (68-107)		84.44±9.12 (68-105)		2.312	<0.05*
*FBI(mIU/L)	12.84±7.2 (3-30)		10.29±5.3 (3.4-25.2)		3.84	<0.001*
*FG/FI ratio	9.51±5.97 (2.6-30.3)		10.09±4.5 (3.5-27.1)		-1.041	>0.05
Insulin sensitivity	87.08±52.6 (23.9-273)		95.53±41.9 (30.4-223.3)		-1.685	>0.05
B-cell function	142.47±58.5 (45.9-340.9)		130.86±45.8 (52.7-298)		2.094	<0.05*
Insulin resistance	1.62±0.9 (0.37-4.18)		1.3±0.67 (0.45-3.29)		3.818	<0.001*
	(n)	**%**	**(n)**	**%**	**X^2**	**P**
+ve *F.H of Diabetes	68	37.78	45	25	6.823	<0.05*
+ve history of macrosomia	22	12.22	33	18.33	2.597	>0.05
Abnormal lipid profile	10	5.56	5	2.78	1.739	>0.05
FG/FI ratio <4.5	47	26.11	21	11.67	12.256	<0.001*

wt=weight, ht.=height, FBS=fasting blood sugar, FBI=fasting blood insulin, FG/FI ratio=fasting glucose-fasting insulin ratio, F.H=family history

Table 2: Relation between family history of DM, abnormal lipid profile, previous macrosomia and the various study parameters

	Family history of D.M		T test		Abnormal lipid profile		T. test		Previous macrosomic baby		T. Test	
	Positive	Negative	t.	*P*	Positive	Negative	t.	*P*	Positive	Negative	t.	*P*
	Mean ±SD	Mean ±SD			Mean ±SD	Mean ±SD			Mean ±SD	Mean ±SD		
Age(yrs)	32.81 ±4.5	28.9 ±5.15	-5.213	<0.001*	37.1 ±3.2	29.97 ±5.1	-4.379	<0.001*	34.2 ±4.4	29.8 ±5.2	-3.772	<0.001*
***Wt.(Kg)**	76 ±12.98	68.7 ±11.6	-3.901	<0.001*	92 ±9.2	70.3 ±11.7	-5.761	<0.001*	84.6 ±8.2	69.7 ±12	-5.646	<0.001*
***Ht.(cm)**	163.97 ±4.35	163.8 ±4.8	-0.408	>0.05	164.8 ±3.3	163.7 ±4.7	-0.707	>0.05	165±5	163.6 ±4.6	-1.308	>0.05
BMI	28.24 ±4.5	25.6 ±3.7	-4.284	<0.001*	33.9 ±2.99	26.2 ±3.9	-6.179	<0.001*	31.16 ±3.4	25.96 ±3.9	-5.907	<0.001*
Abdominal girth(cm)	95.9 ±11.35	89.2 ±10.4	-4.028	<0.001*	108.7 ±8.1	90.1 ±52.6	-5.27	<0.001*	103.3±7.7	90.1 ±10.7	-5.595	<0.001*
***F.B.S(mg/dl)**	91.5 ±9.9	83.9 ±8.66	-5.446	<0.001*	100 ±3.16	85.98 ±9.5	-4.622	<0.001*	96.4 ±7.2	85.4 ±9.4	-5.237	<0.001*
***F.B.I(mIU/L)**	15.4 ±7.38	11.3 ±6.7	-3.908	<0.001*	22.6 ±4.45	12.3 ±6.9	-4.649	<0.001*	19.5 ±6.2	11.9 ±6.9	-4.887	<0.001*
***F.B/F.I ratio**	8.3 ±5.9	10.3 ±5.9	2.194	<0.05*	4.6 ±0.9	9.8 ±6.01	2.732	<0.05*	5.9 ±3.7	10 ±6.1	3.094	<0.05*
Insulin sensitivity	70.67 ±48.8	97.04 ±52.6	3.351	<0.05*	35.3 ±7.5	90.1 ±52.6	3.285	<0.05*	47.2 ±28.5	92.6 ±52.9	3.947	<0.001*
B-cell function	147.37 ±56.3	139.5 ±59.8	-0.876	>0.05	162.4 ±26	141.3 ±59.7	-2.244	<0.05*	157.8 ±43.4	140.3 ±60.1	-1.316	>0.05
Insulin resistance	1.99 ±0.95	1.4 ±0.8	-4.339	<0.001*	3±0.6	1.5 ±0.9	-5.308	<0.001*	2.6 ±0.83	1.45 ±0.8	-5.485	<0.001*

wt=weight, ht.=height, FBS=fasting blood sugar, FBI=fasting blood insulin, FG/FI ratio=fasting glucose-fasting insulin ratio, F.H=family history

There is a significant positive correlation between the abdominal girth in the cases and the fasting blood glucose, fasting blood insulin, insulin resistance and B-cell function while there is a significant negative correlation with the insulin sensitivity and fasting glucose - insulin ratio.

Table 3: Correlations between the age, BMI,Abdominal girth and the various laboratory parameters in the cases.

Correlations						
Cases	**Age(years)**		**BMI**		**Abdominal girth**	
	r	***P*-value**	**r**	***P*-value**	**r**	***P*-value**
Fasting Bl. Glucose	0.240	<0.05*	0.174	<0.05*	0.163	<0.05*
Fasting Bl. insulin	0.208	<0.05*	0.419	<0.001*	0.434	<0.001*
Fasting glucose - insulin ratio	-0.154	<0.05*	-0.308	<0.001*	-0.321	<0.001*
Insulin sensitivity	-0.215	<0.05*	-0.333	<0.001*	-0.343	<0.001*
B-cell function	0.077	>0.05	0.282	<0.001*	0.304	<0.001*
Insulin resistance	0.222	<0.05*	0.429	<0.001*	0.438	<0.001*

There is no significant correlation between the number of miscarriages and the laboratory finding.

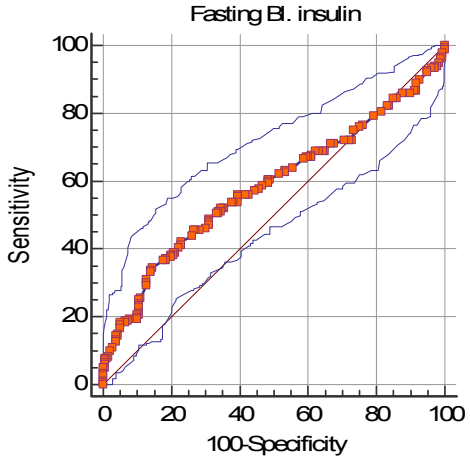
Table 4: Comparison between 1ry and 2ry recurrent miscarriage in cases as regards the demographic and laboratory data.

	Recurrent miscarriage						T-Test	
	1ry			2ry				
	Mean	±	SD	Mean	±	SD	t	*P*-value
Age(years)	28.473	±	5.143	32.379	±	4.606	-5.355	<0.001*
WT (kg)	67	±	11.341	76.264	±	12.147	-5.292	<0.001*
HT (cm)	163.581	±	4.635	164.011	±	4.672	-0.621	>0.05
BMI	24.974	±	3.664	28.318	±	4.103	-5.775	<0.001*
Abdominal girth	87.404	±	10.202	96.334	±	10.473	-5.794	<0.001*
Fasting Bl. Glucose	84.828	±	9.376	88.816	±	9.959	-2.767	<0.05*
Fasting Bl. insulin	10.744	±	6.232	15.080	±	7.530	-4.220	<0.001*
Fasting glucose - insulin ratio	10.755	±	6.049	8.181	±	5.611	2.954	<0.05*
Insulin sensitivity	100.653	±	54.073	72.568	±	47.201	3.702	<0.001*
B-cell function	132.226	±	55.010	153.413	±	60.434	-2.462	<0.05*
Insulin resistance	1.344	±	0.767	1.923	±	0.962	-4.483	<0.001*

Patients with 2ry recurrent miscarriage have got significantly higher BMI,higher abdominal girth, higher fasting blood glucose, higher fasting insulin levels, higher insulin resistance, higher B-cell function, lower insulin sensitivity and lower fasting glucose – insulin ratio in comparison to 1ry recurrent miscarriage.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	-PV
>16.5	33.89	27.0 - 41.3	86.11	80.2 - 90.8	2.44	1.6 - 3.7	0.77	0.7 - 0.9	70.9	56.6

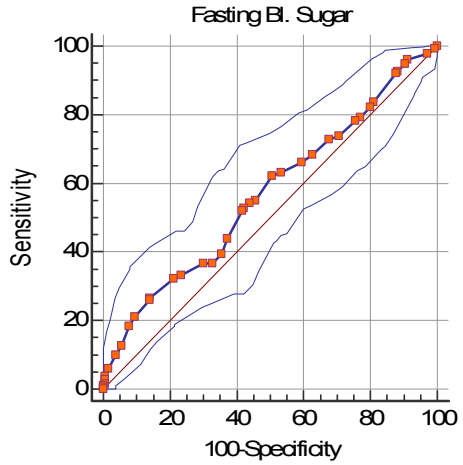
Area under the ROC curve (AUC)	0.585
Standard Error[a]	0.0304
95% Confidence interval[b]	0.532 to 0.636
z statistic	2.789
Significance level P (Area=0.5)	0.0053



Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	-PV
>94	26.67	20.4 - 33.8	86.11	80.2 - 90.8	1.92	1.2 - 3.0	0.85	0.8 - 0.9	65.8	54.0

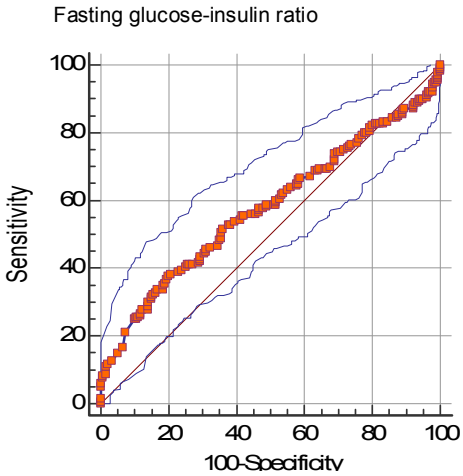
Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.567
Standard Error[a]	0.0302
95% Confidence interval[b]	0.514 to 0.619
z statistic	2.234
Significance level P (Area=0.5)	0.0255



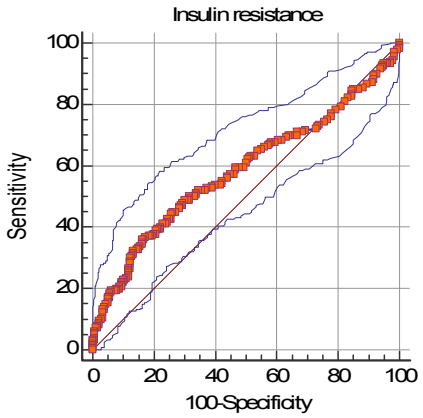
Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	-PV
≤5.9	37.78	30.7 - 45.3	80.00	73.4 - 85.6	1.89	1.3 - 2.7	0.78	0.7 - 0.9	65.4	56.2

Area under the ROC curve (AUC)	0.577
Standard Error[a]	0.0304
95% Confidence interval[b]	0.524 to 0.629
z statistic	2.540
Significance level P (Area=0.5)	0.0111



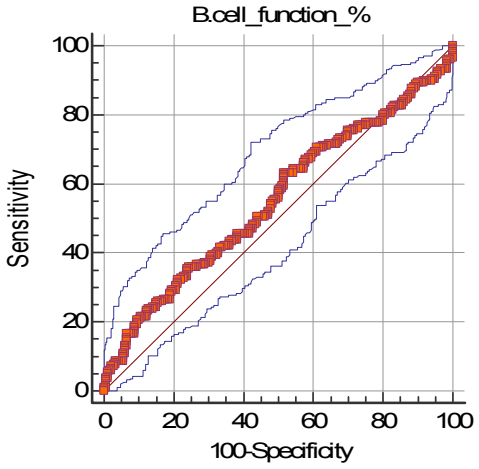
Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	-PV
>2	36.11	29.1 - 43.6	83.89	77.7 - 88.9	2.24	1.5 - 3.3	0.76	0.7 - 0.9	69.1	56.8

under the ROC curve (AUC)	0.584
Standard Error[a]	0.0304
95% Confidence interval[b]	0.531 to 0.635
z statistic	2.760
Significance level P (Area=0.5)	0.0058



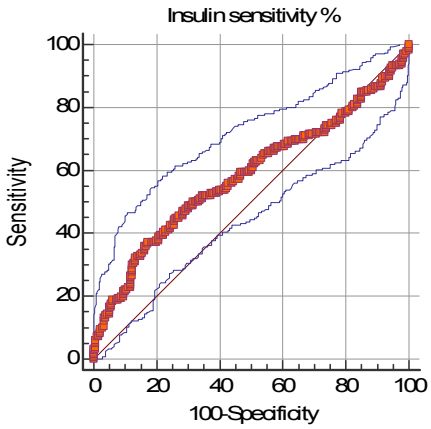
Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	-PV
>118.7	63.33	55.8 - 70.4	48.33	40.8 - 55.9	1.23	1.0 - 1.5	0.76	0.6 - 1.0	55.1	56.9

Area under the ROC curve (AUC)	0.552
Standard Error[a]	0.0305
95% Confidence interval[b]	0.499 to 0.604
z statistic	1.694
Significance level P (Area=0.5)	0.0902



Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	-PV
≤49.8	36.11	29.1 - 43.6	83.89	77.7 - 88.9	2.24	1.5 - 3.3	0.76	0.7 - 0.9	69.1	56.8

under the ROC curve (AUC)	0.583
Standard Error[a]	0.0304
95% Confidence interval[b]	0.530 to 0.635
z statistic	2.730
Significance level P (Area=0.5)	0.0063



4. Discussion:

Although recurrent pregnancy loss is a rare condition and is only found in 1 - 5% of couples desiring pregnancy yet it is considered a very distressing event to the affected patients and a major challenge to the treating physicians [3].

There are many reported causes of recurrent miscarriage, some of them have been well documented, and others are still a matter of discussion. Endocrine and metabolic derangements are considered an important entity in causing miscarriage. PCO have been widely studied as a cause of recurrent miscarriage. It is well established that hyperinsulinemia and insulin resistance have been attributed as a cause of recurrent miscarriage in PCO patients [16].The role of insulin resistance in recurrent unexplained miscarriage is still controversial.

Our study is one of the largest case control studies assessing the role of hyperinsulinemia and insulin resistance in recurrent unexplained 1st trimesteric miscarriage. It showed higher mean fasting blood glucose in cases in comparison to controls (86.76±9.8, 84.44±9.12) (P < 0.05). This was different from the study by Kotanaie *et al.* [17] and a meta analysis done by Li *et al.* [18] assessing 7 clinical trials that showed no significant difference in fasting blood glucose between cases and controls. In another study by Celikn *et al.* [19], their finding were similar to our finding.

Our study showed a significantly higher mean fasting insulin level in cases in comparison to controls indicating hyperinsulinemia in patients with recurrent unexplained miscarriage (12.84±7.2, 10.29±5.3) (P < 0.001). This was similar to all the previous studies [17, 18, 19] and this confirms the importance of hyperinsulinemia as a cofactor for recurrent miscarriage.

Regarding the fasting glucose- insulin (FG-I) ratio, there was no significant difference between the cases & controls (9.51±5.97, 10.09±4.5) (P > 0.05). This is similar to the results of the study done by Craig *et al.*[8] that assessed FG-I ratio as a whole without categorizing it. There was significantly higher number of cases with FG-I ratio <4.5 in comparison to controls in our study (26.11%, 11.67%) (P <0.001). this is different from the study by Kotanaie *et al.*[17] that showed no significant difference. This may be due to the small sample size in the latter study. In a meta analysis done in China by Liz *et al.*[18] including 7 clinical trials with a total number of 467 cases & 413 controls, cases with FG-I ratio <4.5 were more than controls (OR: 3.37, 95% CI: 1.9 to 5.99, P < 0.01).

The mean HOMA insulin resistance (IR) in the cases was significantly higher than the controls (1.62±0.9, 1.3±0.67). These results were similar to the study by Celik *et al.*[19] although he showed that the mean HOMA-IR value was 4.16 in the study group in comparison to 1.62 in the control group which was much higher in comparison to our numbers but this may be attributed to the small sample size they used in their study.

In this study we tried to find out a new cut off value for diagnosing insulin resistance in cases of recurrent unexplained miscarriage. We found a fasting insulin >16.5 µU/ml, fasting blood glucose > 94 mg/dl, FG-I ratio ≤5.9, HOMA IR > 2. They all share the fact that they have got high specificity but low sensitivity. (86.11, 33.89; 86.11, 26.67; 80,37.78;83.89,36.11 respectively). May be larger population based studies on larger number of cases are needed to reach better cut off values.

Conclusion:

Frequency of insulin resistance is significantly high in cases with recurrent unexplained 1st trimestric miscarriage. Insulin resistance may probably be an important cofactor for causing recurrent pregnancy loss.

Recommendations:

We recommend a further study to be done on the cases in this study to assess the effect of Metformin intake during pregnancy to improve the pregnancy outcome.

Conflict of interest: None

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