RELATIONSHIP OF SERUM FASTING INSULIN WITH GONADOTROPINS IN INFERTILE WOMEN

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ABSTRACT

Background: *Infertility has become a global health problem in the world wide affecting 8-10% of couple. It is also a matter of social injustice and inequality. Increase level of insulin has been implicated as a cause of infertility.* ***Objective:*** *To find out the association of fasting serum insulin level with gonadotropins in infertile women.* ***Methods:*** *This cross sectional study was conducted in the department of Physiology, Dhaka Medical College, Dhaka from July 2010 to June 2011. A total number of 150 female age ranged from 20 – 40 years were included in this study. Out of them100 infertile women were selected as study group (group B). Group B was subdivided into group B_1 and B_2. Group B_1 consisted of 50 primary infertile women and group B_2 consisted of 50 secondary infertile women. Rest 50 age matched apparently healthy parous women were considered as base line control group A. All the study subjects were selected from out patient department of infertility unit, BSMMU, Dhaka. The control subjects were selected by personal contact. Serum fasting insulin was measured by enzyme-link-immunosorbend assay. Fasting blood glucose and blood glucose two hours after breakfast were measured by glucose oxidase method. The Data were collected in a prescribed data sheet after taking written consent. Statistical analyses were done by unpaired students "t" tests by SPSS program version 12. The level of significance was calculated and p value <0.05 was accepted as level of significance.* ***Results:*** *In this study, the mean fasting serum insulin level were significantly higher in infertile women than those of fertile women (p<0.001). Within the study group serum fasting insulin was higher in primary infertile women than that of secondary infertile women both were statistically not significant. Again, serum FSH and LH levels were significantly lower (P<.0001) in infertile women than those of fertile women. But serum FSH level was lower and LH level was higher in primary infertile women than that of secondary infertile women. In addition, fasting blood glucose level was almost similar but within normal limits in all groups. Blood glucose 2HABF was significantly higher in secondary infertile women than that of fertile women but within in normal limit. Moreover, fasting serum insulin level was negatively correlated with serum FSH and LH in primary infertility but negatively correlated with serum FSH and positive correlation with serum LH in secondary infertility.* ***Conclusion:*** *From the above study it may be concluded that fasting serum insulin level was higher in infertile women than those of healthy fertile women. These alterations may lead to menstrual irregularities, ovulatory dysfunction and infertility.*

Keywords: *Infertility, Insulin, FSH, LH.*

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INTRODUCTION

Infertility is defined as the inability of couple to conceive after 1 years of frequent unprotected intercourse without contraception.[1,2] Infertility has become a global health problem of twenty first century affecting approximately 8-10% of couple worldwide. The main causes of sub fertility can be due to ovarian factor (30–40 %), cervical factor (5%), male factor (25–40%) and unexplained cause (10–15%).[3] Primary infertility denotes those women who have never conceived. Secondary infertility indicates; conceive previously but failure to conceive subsequently.[4]

A global review of infertility from the world Fertility Survey estimated rates of infertility both primary and secondary approximately 10% in South Asia, 8% in India, 10% in Pakistan, 11% in Sri Lanka, 12% in Nepal and 15% in Bangladesh.[5]

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High level of insulin can be as a metabolic state where normal glucose homeostasis mechanisms fail to operate properly. The American Diabetes Association has characterized hyperinsulinemia or insulin resistance is a state of impaired metabolic response to insulin.[6] To achieve euglycemia, the pancreas over secretes insulin.[7] High level of insulin in infertile women are the risk for metabolic syndrome and coronary artery disease and also lead to an increase risk of miscarriage ,pre- mature birth and birth defects.[8]

Again, increase level of insulin may cause hormonal imbalance in the pituitary gland and ovary. This leads to an increased secretion of lutenizing hormone (LH). Increased LH secretion then causes ovulation disorders, menstrual irregularities and infertility.[9,10]

High level of insulin may be due to reduced number of insulin receptors, insulin resistance, and altered the insulin to receptor interaction or post receptor failure. In infertile women, post receptor defect is the main cause of hyperinsulinemia. High level of insulin may causes hyperandrogenemia and also conversion of androstenedione to estrone. Increase level of estrone level may causes increased prolactin level in 30%-40% patients 3.

Many investigators of different countries reported that high level of insulin may cause increase secretion of androgens (male hormones) in the female which worsen the symptom of infertility. In addition, hyperinsulinemia produces the hyperandrogenism by increasing ovarian androgen production, particularly testosterone and by decreasing the sex hormone binding globulin concentration.[11,12,13] The high level of androgenic hormones interfere with the pituitary ovarian axis, leading to increased LH levels, anovulation, amenorrhea, recurrent pregnancy loss, and infertility.[14,15,16,17.]

Again, increased level of insulin may causes abnormal glucose uptake, impaired glucose tolarence abnormal glucose metabolism and increase basal hepatic glucose production that may lead to increase blood level in infertile women.

Therefore, the present study has been undertaken to measure fasting serum insulin level to evaluate the relationship of gonadotropins (FSH, LH) in infertile women. Hence assessment of serum fasting insulin level are mandatory in all infertile women.

METHODOLOGY

This cross sectional study was carried out in the department of Physiology, Dhaka Medical College, Dhaka from July 2010 to June 2011 and the protocol was approved by Ethical Review Committee of Dhaka Medical College, Dhaka. Female with tubal factor, congenital anomaly of urogenital tract and any obvious organic lesion or pelvic inflammatory diseases, lactating women were excluded from the study. A total number of 150 female age ranged from 20–40 years were included in this study. Out of them100 infertile women were selected as study group (group B) and study subjects were selected from out patient department of infertility unit, BSMMU, Dhaka. Group B was subdivided into group B_1 and B_2. Group B_1 consisted of 50 primary infertile women and group B_2 consisted of 50 secondary infertile women. Rest 50 age matched apparently healthy parous women were considered as base line control group and were selected by personal contact. After selection of the subject the purpose and benefits of the study were explained to each subject and informed written consent was taken from them. A detailed personal, medical, family, socio-economic and drug history were recorded in a prefixed questionnaire foam. Blood were collected from subjecte in 2nd day of menstrual cycle. With all aseptic precaution, five (5) ml of venous blood was drown from medialcubital vien by disposable plastic syringe. Blood was allowed to clot and then centrifuged at a rate of 3000 rpm for 5-10 minutes and supernatant clear serum was separated and preserved at -28° C for estimation of serum insulin, FBG, blood glucose 2HABF, serum FSH and LH. Serum FSH and LH were measured by radioimmunoassay at the laboratory of centre for Nuclear Medicine and Ultrasound, Dhaka Medical College, Dhaka. Fasting serum insulin was measured by ELISA method, fasting blood glucose and blood glucose 2HABF were measured by glucose oxidase method at the laboratory of endocrinology, BIRDEM. Statistical done analysis was done by using statistical package of social service (SPSS) version12. The results were expressed as mean ($\pm$SD). Comparison between two groups were done by using unpaired Students' tests and correlation analysis was done by using Pearson's correlation analysis. The test of significant was calculated and p value $<0.05$was accepted as level of significance.

RESULTS

Anthropometric data of study subjects are presented in Table I. In this study, mean ($\pm$SD) age in different groups were almost similar and no statistically significant differences were observed between the study groups and control group. So the ages were well matched for the study.The mean ($\pm$SD) BMI were significantly higher ($p<0.001$) in group B_1 and B_2 in compression to those of group A. Wherease, there was no significant differences of this value was observed between group B_1 vs B_2. (Table I)

Table-I

Age and body Mass Index (BMI) in different groups

Groups	n	Age (years) Mean±SD	BMI (kg/m^2) Mean±SD
A	50	27.82±4.65	25.35±3.48
B_1	50	27.08±4.15	28.05±4.08
B_2	50	28.98±4.81	27.62±3.68

Statistical analysis

Groups	Age (p value)	BMI (P Value)
A vs B_1	0.404^{ns}	0.001^{**}
A vs B_2	0.2231^{ns}	0.002^{**}
B_1 vs B_2	0.037^{*}	0.580^{ns}

The results are expressed as Mean±SD. Unpaired Student's 't' test was performed to compare between groups. The test of significance was calculated and p values <0.05 was accepted as level of significance.

Group A : Fertile women n = Number of subjects
Group B_1: Primary infertility df = Degree of freedom
Group B_2: Secondary infertility ns = Not significant
* = Significant at P<0.05

The mean (±SD) fasting serum insulin levels were 17.37± 3.05, 20.04 ± 3.46 and 19.13 ± 2.62 μIU/ml in groups A, B_1 and B_2 respectively. In this study, mean (±SD) fasting serum insulin levels were higher in group B_1 and B_2 in comparison to that of group A which were statistically highly significant (P<0.0001). Again, the fasting serum insulin was higher in group B_1 than that of group B_2 but the difference was not statistically significant.(Table-II)

Table-II

Serum insulin levels in different groups

Groups	n	Serum insulin (µIU/ml) Mean±SD
A	50	17.37±3.05
B_1	50	20.04±3.46
B_2	50	19.13±2.62

Statistical analysis

Groups	(p value)	Serum Insuline (P Value)
A vs B_1	0.007^{**}	0.0001^{***}
A vs B_2	0.0001^{***}	0.003^{**}
B_1 vs B_2	0.599^{ns}	0.140^{ns}

The results are expressed as Mean±SD. Unpaired Student's't' test was performed to compare between groups. The test of significance was calculated and p values <0.05 was accepted as level of significance.

Group A : Fertile women n = Number of subjects
Group B_1 : Primary infertility df = Degree of freedom
Group B_2 : Secondary infertility ns = Not significant
** = Significant at P<0.01
*** = Significant at P<0.001

The mean (±SD) fasting blood glucose were 5.44 ± 0.80, 5.64 ± 1.06 and 5.40 ± 0.77 mmol/l in groups A, B_1 and B_2 respectively. In this study, this values were almost similar in all groups and no statistical significant difference were observed among the groups.(Table-III)

The mean (±SD) blood Glucose 2HABF were 6.95 ± 0.85,7.15 ± 1.63, 7.41 ± 0.90 mmol/l in groups A, B_1 and B_2 respectively. The mean (±SD) blood glucose 2HABF was significantly higher in group B_2 than that of control group A.

Whereas, this value were almost similar in group B_1 and B_2 and the difference was not statistically significant. (Table-III)

Table-III

Fasting blood glucose and blood glucose 2HABF in different groups

Groups	n	FBG (mmol/L) Mean±SD	Blood glucose 2HABF (mmol/L) Mean±SD
A	50	5.44±0.80	6.95±0.85
B_1	50	5.64±1.06	7.15±1.63
B_2	50	5.40±0.77	7.41±0.90

Statistical analysis

Groups	FBG (p value)	Blood glucose 2HABF (P Value)
A vs B_1	0.289^{ns}	0.439^{ns}
A vs B_2	0.808^{ns}	0.010^{*}
B_1 vs B_2	0.201^{ns}	0.331^{ns}

The results are expressed as Mean±SD. Unpaired Student's't' test was performed to compare between groups.The test of significance was calculated and p values <0.05 was accepted as level of significance.

Group A : Fertile women
Group B_1: Primary infertility
Group B_2: Secondary infertility

n = Number of subjects
df = Degree of freedom
ns = Not significant
** = Significant at P<0.01
*** = Significant at P<0.001

The mean (±SD) serum FSH level were 6.48 ± 3.83, 3.73 ± 2.03 and 4.66 ± 2.23 IU/l in groups A, B_1 and B_2 respectively. In this study, the mean (±SD) serum FSH levels were significantly (P<.0001) lower in group B_1 and B_2 in comparison to those of control group A. Again, serum FSH level was lower in group B_1 than that of group B_2 but the difference was also statistically significant. (Table-IV)

The mean (±SD) value of serum LH levels were 8.37 ± 5.16, 4.86 ± 3.15 and 3.47 ± 2.03 IU/l in groups A, B_1 and B_2 respectively. The mean (±SD) serum LH level was significantly (P<0.0001) lower in group B_1 and B_2 in comparison to those of group A. Again, this value was also significantly lower in group B_2 than that of group B. (Table-IV)

Table-IV

Serum FSH and LH levels in different groups

Groups	*n*	*Serum FSH (IU/L) Mean±SD*	Serum LH (IU/L) Mean±SD
A	50	6.48±3.83	8.37±5.16
B_1	50	3.73±2.03	4.86±3.15
B_2	50	4.66±2.23	3.47±2.03

Statistical analysis

Groups	Serum FSH (p value)	Serum LH (P Value)
A vs B_1	0.0001^{***}	0.0001^{***}
A vs B_2	0.005^{**}	0.0001^{***}
B_1 vs B_2	0.032^{*}	0.011^{*}

The results are expressed as Mean±SD. Unpaired Student's 't' test was performed to compare between groups. The test of significance was calculated and p values <0.05 was accepted as level of significance.

Group A : Fertile women
Group B_1: Primary infertility
Group B_2: Secondary infertility

n = Number of subjects
df = Degree of freedom
* = Significant at P<0.05
** = Significant at P<0.01
*** = Significant at

Pearson's correlation coefficient (r) was performed to observe the relationship of serum prolactin and Fasting serum insulin with different study parameter in different group. **Relationship of Fasting serum insulin with FBG, serum FSH and LH in different group**

Correlation of fasting serum insulin with fasting serum blood glucose:
The fasting serum insulin level showed non significant positive correlation with fasting serum glucose in group A (r = + 0.141) and B_1 (r = + 0.147). In group B_2, fasting serum insulin was positively correlated (r=+0.356) with fasting serum glucose which was statistically significant.

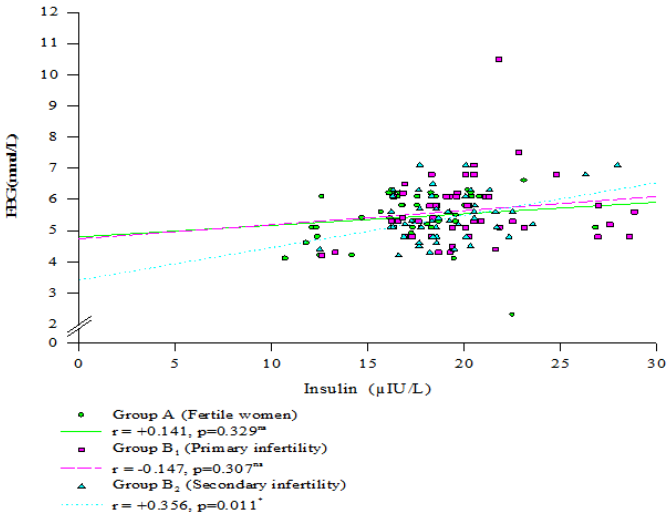

Fig-1: Correlation between serum insulin and FBG in different groups

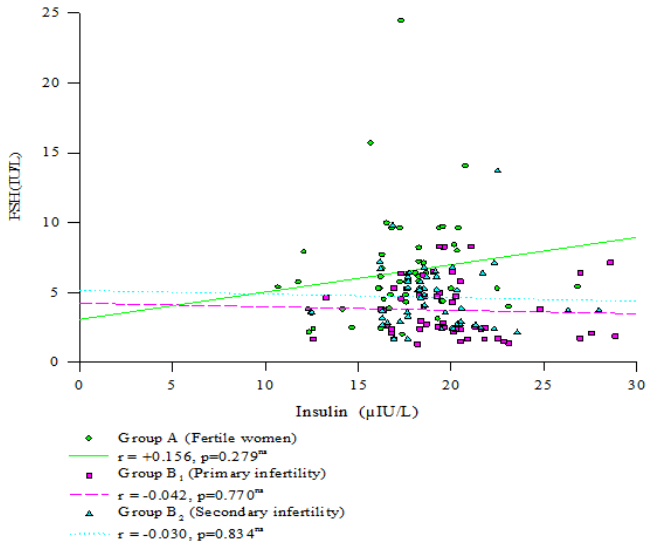

Fig 2 : Correlation of fasting serum insulin with serum FSH

Correlation of fasting serum Insulin with serum FSH

The fasting serum insulin levels showed negatively correlated with serum FSH in group B_1(r = - 0.042) and B_2 (r = - 0.030) which were statistically not significant but positive correlation with serum FSH in group A (r = + 0.156) which was also statistically not significant. (Fig- 2)

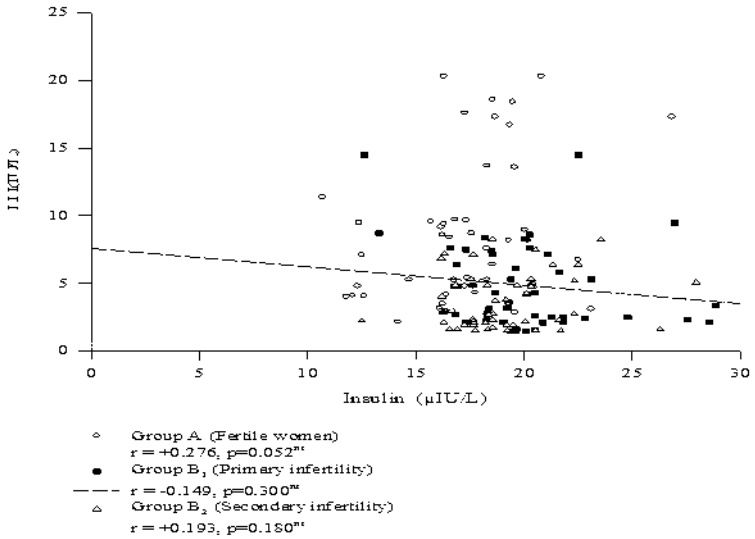

Fig 3 : Correlation of fasting serum insulin with serum LH

Correlation of fasting serum insulin with serum LH

In this study, the fasting serum insulin level showed negatively correlated with serum LH insulin in group B_I which was statistically not significant. But positive correlation with serum LH in group A (r = + 0.276) and B_2 (r = + 0.193) which were also statistically not significant (Fig-3).

DISCUSSION

In this study, the mean serum fasting insulin level was significantly higher (p< 0.05%) in infertile women than that of control fertile women. This finding is in agreement with that of some other researchers.[15-19] Again, serum fasting insulin was higher in primary infertile women than that of secondary infertile women which was statistically not significant. Many researchers of different countries observed positive correlation between serum fasting insulin and infertility.[15-19]

Serum fasting insulin level was non significant positively correlated with FSH in fertile women but non significant negative correlation in both primary secondary infertile women. These observations are in consistant with those of other research workers of different countries. Again, serum fasting insulin level was positively correlated with LH in fertile women and secondary infertile women but negatively correlated in primary infertile women. All these values were statistically not significant. Similar findings were also made by other investigators.[9-12]

Moreover the mean serum FSH and LH were significantly lower in infertile women than that of control fertile women are similar to the finding made by other research workers of different countries .However, serum FSH was significantly lower in primary infertile women than those of secondary infertile women. On the other hand, serum LH was significantly lower in secondary infertile women than that of primary infertile women. Similar observation was made by other research workers.[9-18]

In this study, the mean fasting blood sugar was almost similar in infertile women and fertile women. No statistically significant differences were observed among them. Again, the mean blood glucose 2HABF were significantly higher in infertile women than that of fertile women. This finding is in agreement with those of other investigator.[9-18] Some investegators reported that high level of insulin may causes excess hepatic glucose production, which reflect hepatic hepatic insulin resistance. Hyperinsulinemia in nomoglycemic adults are risk factor for developing dysglycemia (impaired fasting blood glucose, glucose tolarence or type -2 diabaties).

Many investigators of different countries reported that high level of insulin may cause increase secretion of androgens (male hormones) in the female which worsen

the symptom of infertility. In addition, hyperinsulinemia produces the hyperandrogenism by increasing ovarian androgen production, particularly testosterone and by decreasing the serum sex hormone binding globulin concentration. The high levels of androgenic hormones interfere with the pituitary ovarian axis, leading to increased LH levels, an ovulation, amenorrhea, recurrent pregnancy loss and infertility.[9-18]

Some investigators suggested that hyperinsulinemia inhibites hepatic synthesis of SHBG which may causes infertility. Decrease level of SHBG may causes increases testosterone and estrogen level. Increased estrogen section causes increased LH and decreased FSH level. Suboptimal FSH action leads to follicular stimulation but no maturation or ovulation. As a result numerous small and immature follicles undergo atresia and also prevents normal follicular growth and causes premature follicular atresia which leads to anovulatory cycle and infertility[9-18].

CONCLUSION

From the present study, it may be concluded that infertile women had significantly higher fasting serum insulin level than that of healthy fertile women. High level of insulin may have some role in decreasing serum FSH and LH which may be due to increase secretion of androgen from ovarian theca cell resulting anovulatory infertility.

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