Original Article

PROLACTIN AND INSULIN ESTIMATES IN PREGNANCY WITH GLUCOSE INTOLERANCE

Mohammed H. Shalayel[1], Mohammed S. Elrobh[2], Saadeldin A. Idris[3], Mohammed S Mohammed[4], Salah A Ahmed[5]

ABSTRACT

Objective: To show the relation of prolactin with the incidence of glucose intolerance in pregnancy.

Methodology: This study was carried out on thirty Sudanese pregnant ladies suffering from gestational diabetes mellitus, 30 ones with impaired glucose tolerance and 30 control ones with normal glucose tolerance. All subjects overnight fasted before the test. A fasting blood sample was drawn at 6.00 a.m. Thereafter, 75g oral glucose dissolved in 200 cc water was given for each, waiting for two hours and then another blood sample was drawn. Fasting and 2-h, after 75g glucose load, plasma glucose concentrations (FBS and 2h-BS) were estimated by glucose oxidase method. The concentrations of serum insulin in the fasting sample (0 min.) and in the 2 hour after 75g glucose load sample (120 min.) were measured with a specific immunoradiometric assay. The concentrations of serum prolactin (120 min.) were measured with a specific radioimmunoassay.

Results: There were no significant differences among levels of fasting serum insulin of the three studied groups ($p>0.05$) while, the mean level of 2h- serum insulin of the GDM group was significantly lower than that of the IGT and control groups ($p <0.005$). Results of serum prolactin of the control group in the first, second and third trimester showed that prolactin increases progressively as pregnancy advances ($p <0.0001$). Results of serum prolactin of the GDM, IGT and control groups in the third trimester showed that no two groups were significantly different ($p>0.05$) although the control group recorded the highest mean level of serum prolactin.

Conclusion: Prolactin increases progressively as pregnancy advances, reaching a peak in the third trimester when many pregnant ladies may develop gestational diabetes due to the state of insulin resistance which may occur although there is no evidence that prolactin may be directly incorporated with the pathogenesis of glucose intolerance in pregnancy. A decline in insulin secretion may lead to a decline in prolactin since insulin stimulates both acute secretion and de novo synthesis of decidual prolactin.

KEY WORD: Gestational diabetes mellitus (GDM), Impaired glucose tolerance (IGT), Insulin, Prolactin (PRL).

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Correspondence:

Mohammed H. Shalayel
E-mail: drmhfs@hotmail.com

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INTRODUCTION

Prolactin (PRL) or mammotropic hormone is a protein hormone with a molecular weight of about 23kDa[1] contains 199 amino acid residues and three disulfide bridges and has consider-

able structural similarity to human growth hormone and human chorionic somatomammotropin (hCS). The half-life of prolactin like that of growth hormone, is about 20 minutes.[2] It is secreted by lactotrophs, which are acidophilic cells in the anterior pituitary. Prolactin (PRL)–secreting lactotrophs, which normally constitute up to 20% of cells in the pituitary in both men and nulliparous women, increase to comprise up to 50% of pituitary cells at the end of pregnancy. They are large, mitotically active, and display increased immunoreactivity for prolactin. This lactotroph hyperplasia is believed to be secondary to multiplication of pre-existing mature lactotrophs and recruitment of inhibited somatotrophs (reduced growth hormone [GH] messenger RNA [mRNA] content) to become mammosomatotrophs. The hyperplasia is related to the direct effect of increasing estrogen secretion and action.[3]

The number of these cells and their size increase dramatically during pregnancy.[1] Prolactin causes milk secretion from the breast after estrogen and progesterone priming. Its effect on the breast involves increased action of mRNA and increased production of casein and lactalbumin. Prolactin also inhibits the effects of gonadotropins, possibly by an action at the level of ovary. It also has a role in preventing ovulation in lactating women.

The normal plasma prolactin concentration is approximately 8 ng/ml in women[2] but during pregnancy, it rises several fold and the number and size of lactotropic cells increase.[4] Prolactin has important biological actions, which include metabolic control and water/electrolyte balance in several species. Noteworthy among these effects has been the suggestion that prolactin is diabetogenic. Administration of an ovine prolactin preparation induced diabetes mellitus in partially pancreatectomized cats and doges. Subsequent studies in normal doges given ovine PRL, demonstrated changes in glucose and free fatty acids metabolism. However, in human, prolactin has generally been characterized as a mammotropic hormone and it is largely unknown as to whether it has any other relevant biological action. In particular, previous data are quite conflicting in concerning the effect of prolactin on human glucose metabolism.[5]

Gestational diabetes mellitus (GDM) is defined as "carbohydrate intolerance of varying severity with onset or first recognition during pregnancy;[6-8] this does not encompass women who are known to have diabetes prior to conception.[9] This definition applies whether insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy.[10-12]

The prevalence of GDM varies worldwide, comprising from 1% to 14% of all pregnancies depending on the population studied and the diagnostic tests employed.[13] We aimed in this study to show if there is a relation between prolactin as insulin antagonistic hormone and incidence of glucose intolerance in pregnancy.

METHODOLOGY

Thirty pregnant women with gestational diabetes mellitus (GDM) and thirty ones with impaired glucose tolerance (IGT) were selected from Khartoum north hospital, Khartoum teaching hospital, Soba hospital, Ibrahim Malek hospital, Maternity hospital and Fath-Elrahman Elbasheer referral centre for this study. They were all discovered in the third trimester of pregnancy. Diagnostic criteria for GDM and IGT were according to the recommendations of the World Health Organisation (WHO) Expert Committee on Diabetes Mellitus. The WHO recommended that an oral load of 75g glucose should be used for glucose tolerance testing.[14] The diagnostic criteria for IGT is a fasting blood glucose ^{3} 6 but < 7.8mmol/l and/or 2h-blood glucose > 7.8mmol/l and < 11.1mmol/l[15] while the WHO defined diabetes in pregnancy as a fasting glucose level of > 7.8 mmol/l, or a value > 11.1 mmol/l 1-2 hours following a 75g glucose load.[16] Thirty pregnant women with normal glucose tolerance were chosen as a control group and were followed up through all the three trimesters.

All subjects overnight fasted before the test. A fasting blood sample was drawn at 6.00 a.m. Thereafter, 75g oral glucose dissolved in 200 cc water was given for each, waiting for two hours and then another blood sample was drawn. Fasting and 2-h, after 75g glucose load, plasma glucose concentrations (FBS and 2h-BS) were estimated by glucose oxidase method.[17] The concentrations of serum insulin in the fasting sample (0 min.) and in the two hour after 75g glucose load sample (120 min.) were measured with a specific immunoradiometric assay.[18] The concentrations of serum prolactin (120 min.) were measured with a specific radio immunoassay.[19]

Data Analysis: Results were expressed as means ± SEM. Comparisons were made using analysis of variances (one way ANOVA). Scheffe test with significance level 0.05 was done to show the significant difference between the mean values. Calculations were performed using Statistical Packages for Social Sciences (SPSS) program.

RESULTS

The GDM women were found to have higher mean levels of plasma glucose when compared with the IGT and the control pregnant women as shown in Table-I ($p<0.0001$). There were no significant differences among levels of fasting serum insulin of the three studied groups ($p > 0.05$) while, the mean level of 2h-serum insulin of the GDM group was significantly lower than that of the IGT and control groups ($p < 0.005$).

Results of serum prolactin of the control group in the first, second and third trimester (Table-II) showed that prolactin increases progressively as pregnancy advances ($p < 0.0001$). Results of serum prolactin of the GDM, IGT and control groups in the third trimester (Table-II) showed that no two groups were significantly different at the 0.05 level according to Scheffe test indication ($p > 0.05$) although the control group recorded the highest mean level of serum prolactin and the GDM group recorded the lowest mean level of serum prolactin.

DISCUSSION

Many previous studies have shown that pregnancy results in a state of insulin resistance and ladies with gestational-onset diabetes appear to have a greater degree of insulin resistance.[20,21] The insulin resistance appears to result from a combination of increased maternal adiposity and the placental secretion of hormones (progesterone, cortisol, placental lactogen, prolactin and growth hormone.[21,22] This insulin resistance mainly presents as a hyperinsulinemia.[21,23] To overcome this insulin resistance, most pregnant ladies increase their insulin secretion and this explain the higher levels of fasting and 2h-serum insulin of the IGT group when compared with the normal control group.

However, when the capacity of insulin secretion is not sufficiently large to meet the resistance, glucose intolerance develops and the pregnant ladies will develop gestational diabetes.[21,24]

The present study (on control group) demonstrated that prolactin increases progressively from the first trimester through till third trimester. Moreover, our study revealed that there

Table-I: Results of the studied groups

	FBS (mmol/l)	*2h-BS (mmol/l)*	*Fasting serum insulin (µIu/ml)*	*Serum insulin (120 min)*	*Serum prolactin (ng/dl)*
Control	2.92 + 0.079	4.35 + 0.12	12.39 + 2.52	54.88 + 8.15	150.23 + 9.70
IGT	5.90 + 0.082**	7.98 + 0.13**	14.93 + 2.17	68. 00 + 6.71*	144.3 + 14.99
GDM	7.47 + 0.34***	12.35 + 0.57***	12.29 + 0.83	36.50 + 3.06**	123. 60 + 9.61

All data are expressed as mean + SEM.
*Significant difference as compared with control group ($p<0.05$)
** ($p<0.005$), *** ($p<0.0001$).

Table-II: Serum prolactin results of the control group.

Trimester	*Serum Prolactin (ng/dl)*
First	27.57 + 4.092
Second	74.14 + 9.754**
Third	0.23 + 9.703***

All data are expressed as mean + SEM.
** ($p<0.005$) when compared with serum prolactin level in the first trimester.
*** ($p<0.0001$) when compared with serum prolactin level in the first trimester.

were no significant differences among the levels of serum prolactin in GDM, IGT, and control groups. This agrees with what has been mentioned by Grigorakis *et al*.[22] Consequently, there is no evidence that prolactin may be directly incorporated with the pathogenesis of glucose intolerance in pregnancy. This may agree with the study of Milasinovic *et al*[25] who showed that there is no evidence of the functional connection between prolactin and glucose metabolism.

Prolactin is found in large amounts in the amniotic fluid of humans and other primates, and it is now clearly established that the source of this prolactin is the placenta rather than the maternal or fetal pituitary. The endometrial lining of the uterus is greatly modified during pregnancy to form the decidua. This decidual tissue has been confirmed as the site of placental prolactin production by a number of different groups and the mature peptide hormone is immunologically indistinguishable from pituitary prolactin. Immunocytochemical studies have shown that the hormone is predominantly located in the parietal decidual cells and only very rarely in the chorionic cytotrophoblast. Amniotic fluid prolactin levels are very low in ectopic tubal pregnancy, confirming the role of the decidualized endometrium.[4]

Amniotic fluid prolactin levels rise progressively after the 14th week human gestation and decline somewhat during the 3rd trimester. Prolactin secretion by the deciduas appears to be regulated quite differently from that in the pituitary gland. The first striking difference in regulation is that dopamine and dopamine agonists drugs have no inhibitory effect on decidual prolactin secretion or amniotic fluid prolactin levels. Oestrogen exerts a strong stimulation on pituitary lactotrophs but appears at most to have only small effects on decidual prolactin production.[4]

The very high levels of circulating estrogen during pregnancy result in a parallel increase in the circulating levels of prolactin in pregnancy. The prolactin increase is to prepare the breasts for lactation. Prolactin levels begin to rise at 5-8 weeks of gestation and parallel the increase in the size and number of lactotrophs.[26,27] The resulting high levels of prolactin secretion cause further maturation of the mammary glands, preparing them for lactation.[28]

Progesterone appears to stimulate decidual prolactin secretion although it has little or no effect on decidual cells obtained in early pregnancy. Insulin stimulates both acute secretion and de novo synthesis of decidual prolactin.[4] This may explain why prolactin mean level was the lowest in the GDM group as the level of insulin, which stimulates prolactin secretion, is the lowest when compared with the other groups (the IGT and the control groups).

CONCLUSION

Prolactin increases progressively as pregnancy advances, reaching a peak in the third trimester when many pregnant ladies may develop gestational diabetes. Gestational diabetes occurs when the capacity of insulin secretion is not sufficiently large to meet the state of insulin resistance that occurs in such period of pregnancy.

Therefore, a decline in insulin secretion may lead to a decline in prolactin since insulin stimulates both acute and de novo synthesis of decidual prolactin. This may explain why prolactin mean level was the lowest in the GDM group as the level of insulin, which stimulates prolactin secretion, was the lowest when compared with the other groups of the study.

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Authors:

1. Mohammed H. Shalayel, MBBS, M.Sc., PhD
   National College for Medical and
   Technical Studies, Khartoum, Sudan
2. Mohammed S. Elrobh, M.Sc., PhD
   Department of Biochemistry, Faculty of Science,
   Ain Shams University, Egypt.
3. Saadeldin A. Idris, MBBS, MRCS
   Faculty of Medicine, Western Kordufan University,
   Elnihood, Sudan.
4. Mohammed Siddig Mohammed M.Sc., PhD
   Sudan Atomic Energy Commission,
   P.O. Box 3001. Khartoum. Sudan.
5. Salah A. Ahmed, MBBS, PhD
   Department of Biochemistry,
   Faculty of Medicine,
   University of Khartoum, Sudan.