Physiological effects of prolactin on early pregnancy loss

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Abstract

Abortion generally presented as two types; the spontaneous and the induced abortion. Spontaneous one is the termination of pregnancy before fetal viability which occurs spontaneously. About 80% of spontaneous abortion losses occur in the first trimester, the incidence decreases with advance in pregnancy. Prolactin is a polypeptide hormone that is synthesized in and secreted from specialized cells of the anterior pituitary gland, the lactotrophs. The major action of prolactin is lactogenesis (milk production). It is the major hormone stimulating the production of milk. Prolactin seems to play an important role in implantation and subsequent placentation in the human endometrium, and it is recognized as a crucial signal for the initiation and maintenance of decidualization. In addition to that, prolactin inhibits the secretion of gonadotropin releasing hormone by the hypothalamus, and this inhibition lead to decreased secretion of luteinizing hormone (LH), which normally initiates ovulation, therefore with hyperprolactinemic state ovulation, does not occur (anovulation). The aim of this study is to study the effects of prolactin hormone in the incidence of abortion cases in first trimester pregnancy in women in Tikrit city. Serum Prolactin was measured by using kit made in France. VIDAS Prolactin (Made in Italy), for the enzyme immunoassay determination of human prolactin in human serum or plasma by using the technique of Enzyme Linked Fluorescent Assay (ELFA). One hundred and thirty four pregnant women were participated & finished the whole study; 56 normal pregnant women in first trimester as a control group and 78 women with different types of abortion in first trimester who are diagnosed by clinical examination and/or by ultrasonography as aborted group. Seventy eight aborted women were participating in the present study. Threatened abortion was the highest one among aborted women (44.9%). Followed by missed abortion (19.23%), incomplete abortion (14.1%), complete (9%), inevitable (7.69%) & the last is recurrent (2.57%). Regarding serum prolactin, there is a significant difference between normal pregnant women (47.1 ± 25.4 ng/ml) as compare with aborted women (69.4 ± 48.8 ng/ml). In another word, aborted women have a serum prolactin concentration than that of normal pregnant women ($p \leq 0.01$).

Key words: *Prolactin, women, abortion, age group.*

Introduction

Abortion is defined as termination of pregnancy by expulsion from the uterus of fetus or embryo before fetal viability outside the uterus, (20-24 weeks of pregnancy) with a fetus born weighing less than 500 gram, (1-3). World Health Organization (WHO) defines abortion as pregnancy termination prior to 20 weeks gestation or a fetus born less than 500gm, (4). The period of gestation between 6-9 weeks is known as the embryonic period while the period from 10 weeks until delivery represents the fetal period, (5-6). In first trimester miscarriages, important causes include chromosomal abnormalities, which occur in about 60-70% of the cases, maternal diseases, including poorly-controlled diabetes mellitus, uncontrolled thyroid disease, severe systemic lupus erythematosus and antiphospholipid syndrome, (7-9). Poor maternal lifestyle habits like, alcohol consumption, smoking and use of illicit drugs, in addition to exposure to non-steroidal anti-inflammatory drugs (NSAIDs) around the time of conception, (10-11). The emotional response to miscarriage which includes anxiety, depression, denial, anger, and a sense of loss, sleep disturbance, and marital disturbances might have profound effects on maternal health, (12-13). About 80% of spontaneous abortion losses occur in the first trimester, the incidence decreases with advance in pregnancy, (1-2). Regarding to the induced one it means the termination of an intact pregnancy before reaching the time of viability outside the mother, (7). Prolactin is a polypeptide hormone that is synthesized in and secreted from specialized cells of the anterior pituitary gland, the lactotrophs, (14). The major action of prolactin is lactogenesis (milk production). It is the major hormone stimulating the production of milk. Prolactin seems to play an important role in implantation and subsequent placentation in the human endometrium, (15-18), and it is recognized as a crucial signal for the initiation and maintenance of decidualization, (13-17). Therefore, it has been proposed that decidual PRL promotes blood vessel development in the placenta, (16). In addition to that, prolactin inhibits the secretion of gonadotropin releasing hormone by the hypothalamus, and this inhibition lead to decreased secretion of luteinizing hormone (LH), which normally initiates ovulation, therefore with hyperprolactinemic state ovulation does not occur (anovulation); without ovulation, fertilization and pregnancy are impossible, (19-21). The aim of this study is to study the effects of prolactin hormone in the incidence of abortion cases in first trimester pregnancy in women in Tikrit city.

Subjects and methods

This study was carried out during a period extending from November 2011 to May 2012 in gynecological unit in Tikrit Teaching Hospital. One hundred and fifty six pregnant women at first trimester participated in this study. A special questionnaire form was arranged and full information were collected and the clinical details were recorded from each pregnant women which include: name, age, address, parity, gravidity, last menstrual period (L.M.P.), the main presenting symptoms and past obstetric history related to poor previous obstetric outcomes (previous abortions, stillbirth and preterm delivery) or cesarean delivery or any gynecological operations. Related medical history was also recorded particularly hypertension, diabetes, acute and chronic infections to exclude subjects with history of any systemic diseases. The gestational age was calculated from the last menstrual period and by ultrasonogrphy. Finally, the total

subjects who finished the measurement are one hundred and thirty four pregnant women that included; 56 normal pregnant women in first trimester as a control group and 78 women with different types of abortion in first trimester who are diagnosed by clinical examination and / or by ultrasonography as a diseased group. Twenty two subjects were exclude from the study for the following reasons – Eleven pregnant women with positive TORCH test, 4 pregnant diabetic women, 3 pregnant women with hypertensive state and other 4 pregnant women with high body temperature. Body height was measured to the nearest one centimeter & body weight was measured by electronic scale, the women measured without shoes. Body mass index (BMI) was calculated, from body weight (kg), divided by height square (cm^2). Heart rate was measured by pulse meter (Sanyo, Japan) for one minute at resting state & blood pressure was taken by the indirect method (auscultatory method) by the means of sphygmomanometer, after 10 minutes resting time. About 8 ml blood was drawn from each participant using a tourniquet, before any medical or surgical interference regarding the abortion cases. One ml of blood placed into an EDTA tube and mix gently for further hematological counts, and the other blood sample was put into plan tube without anticoagulant for serum separation. The serum was divided into 3 separated plastic tubes, one for biochemical analysis, the second for TORCH test and the other for hormone analysis. The biochemical analysis (blood sugar) and TORCH are done immediately, while the other serum stored in a deep freeze (-18°C) for further analysis.

Prolactin was measured by using kit made in France. VIDAS Prolactin (PRL) is an automated quantitative test for use on the VIDAS family instruments (Made in Italy), for the enzyme immunoassay determination of human prolactin in human serum or plasma by using the technique of Enzyme Linked Fluorescent Assay (ELFA), (21). ***Estrogen was measured by using*** the kit used for this test (22), & was from Roche (Germany) which was used on cobas e 411 analyzers – disk system, from Roche Diagnostic (Germany).***Also, progesterone was measured according standred procedure (22), by using*** the kit used for this test was from Roche (Germany) which was used on cobas e 411 analyzers –disk system, from Roche Diagnostic (Germany). Inhibin was measured according standred procedure, (23-24). Inhibin A tested in this study by Enzyme Linked Immune Sorbent Assay (ELISA) (product of Human Com. Made in Germany) .The kit used for this test was enzyme linked immunosorbent assay kit from BECKMAN COULTER (USA). Statistical analysis was done by using unpaired T test. Significant values at 0.05 & 0.01 were accepted as significant values. All data were presented as a mean & standard deviation (SD).

Results

One hundred and thirty four pregnant women were participated & finished the whole study; 56 normal pregnant women in first trimester as a control group and 78 women with different types of abortion in first trimester who are diagnosed by clinical examination and/or by ultrasonography as aborted group. Table 1 shows the mean & standard deviation of age, body weight, height, cardiac parameters, body temperature & fasting or random blood sugar. In another words, normal healthy pregnant women are match aborted women for all measured parameters. Table 2 shows that there is significant difference regarding

hemoglobin concentration between normal pregnant women & aborted women ($p \leq 0.05$). However, there are no significant differences regarding red blood corpuscle count & white blood cells count between normal pregnant women & aborted women, (table 2). Table 3 classifies the total aborted women according to the type of abortion. Seventy eight aborted women were participating in the present study. Threatened abortion was the highest one among aborted women (44.9%). Followed by missed abortion (19.23%), incomplete abortion (14.1%), complete (9%), inevitable (7.69%) & the last is recurrent (2.57%). Table 4 shows the serum concentrations of prolactin, inhibin A, estrogen E2 & progesterone in normal pregnant women & aborted women. Regarding serum prolactin, there is a significant difference between normal pregnant women (47.1 ± 25.4 ng/ml) as compare with aborted women (69.4 ± 48.8 ng/ml). In another word, aborted women have a serum prolactin concentration than that of normal pregnant women ($p \leq 0.01$). Regarding serum inhibin A, there is a significant difference between normal pregnant women (214 ± 135 pg/ml) as compare with aborted women (56.1 ± 38.8 pg/ml). In another words, aborted women have a significant reduction in serum inhibin A concentration than that of normal pregnant women ($p \leq 0.01$). Regarding serum estrogen E2, there is a significant difference between normal pregnant women (1103 ± 996 pg/ml) as compare with aborted women (183 ± 56 pg/ml). In another words, aborted women have a significant reduction in serum estrogen E2 concentration when compare with normal pregnant women ($p \leq 0.01$). Table 4 also shows, that, there is a significant difference regarding serum progesterone between normal pregnant women (27.6 ± 13.5 pg/ml) as compare with aborted women (10.2 ± 6.1 pg/ml). In another words, aborted women have a significant reduction in serum progesterone concentration than that of normal pregnant women ($p \leq 0.01$). Table 5 shows that serum prolactin of aborted women & normal in different age groups. There is significant increase in serum prolactin at age group < 20 years of aborted women (86.3 ± 58.9 ng/ml) as compare with normal pregnant women of same age group (45.8 ± 20.6 ng/ml), ($p \leq 0.05$). Moreover, table 5 also shows that there is significant increase in serum prolactin at age group 20-29 years of aborted women (65.9 ± 42.1 ng/ml) as compare with normal pregnant women of same age group (51 ± 27.1 ng/ml), ($p \leq 0.05$). Also, there is significant increase in serum prolactin at age group 30-39 years of aborted women (69.6 ± 58.2 ng/ml) as compare with normal pregnant women of same age group (38.7 ± 25.4 ng/ml), ($p \leq 0.05$). Table 9 shows the serum concentration of prolactin in normal pregnant women & aborted women. Also, there is significant increase in serum prolactin in prime aborted women (89.6 ± 57.6 ng/ml) as compare with normal prime pregnant women (53.3 ± 25.4 ng/ml), ($p \leq 0.05$). The serum prolactin concentration of aborted women (multi pregnant) shows a significant increase in serum prolactin concentration (64.3 ± 41.5 ng/ml) as compare with normal multi pregnant women (50.7 ± 26.3 ng/ml), ($p \leq 0.05$). However, table 6 show no significant differences in regard to serum prolactin concentration between grand multi aborted women (38.7 ± 23.6 ng/ml), as compare with grand multi normal pregnant women (32.6 ± 18.4 ng/ml). Table 7 shows serum concentration of prolactin according to type of abortion. The highest concentration of serum prolactin is in patients with inevitable abortion & the lowest serum prolactin concentration is in aborted patients with recurrent

abortion. There is significant increase in serum prolactin concentration in patients with threatened, inevitable, incomplete, missed & complete abortion as compare with recurrent abortion, ($p \leq 0.01$).

Table (1): Characteristic features of normal & aborted women.

Parameters	Normal (n=56)	Abortion (n=78)	P value
Age (years)	25.96 ± 6.67	26.69 ± 6.5	**NS**
Body weight (kg)	68.357 ± 12.82	67.94 ± 12.7	**NS**
Body height (cm)	157.821 ± 5.17	157.19 ± 5.09	**NS**
BMI	27.469 ± 5.23	27.53 ± 5.2	**NS**
Heart rate (beats/min.)	86.393 ± 5.59	88.65 ± 7.4	**NS**
Systolic BP (mm Hg)	113.84 ± 11.11	109.07 ± 12.3	**NS**
Diastolic BP(mmHg)	70.36 ± 9.5	67.43 ± 9.9	**NS**
Body temperature (C°)	37.254 ± 0.236	37.37 ± 0.222	**NS**
FBS (mg/dl)	70.569 ± 13.5	83.86 ± 13.67	**NS**
RBS (mg/dl)	86.272 ± 16.81	91.85 ± 13.98	**NS**

Table (2): The Mean & Standard Deviation of the hemoglobin, white blood cells and red blood cells in normal and aborted women.

Parameters	Normal (n=56)	Abortion (n=78)	P value
Hb (g/dl)	12.553 ± 0.967	11.95 ± 1.33	<0.01
RBC 10^6/ µl	4.454 ± 0.458	4.505 ± 0.484	NS
WBC 10^3/µl	8.41 ± 2.05	8.36 ± 2.17	NS

Table (3): Aborted women distributed according to types of abortion

Type of abortion	Number	%
Threatened	35	44.87
Inevitable	6	7.69
Complete	9	11.54
Incomplete	11	14.10
Missed	15	19.23
Recurrent	2	2.57
Total	78	100

Table (4): The Mean & Standard Deviation of Serum Prolactin, Inhibin A, Estrogen and progesterone in normal & aborted women

Parameters	Normal Women (56)	Aborted Women (78)	P value
Prolactin (ng/ml)	47.1 ± 25.4	69.4 ± 48.8	<0.01
Inhibin A(pg/ml)	214 ± 135	56.1 ± 38.8	<0.01
Estrogen (pg/ml)	1103 ± 996	183 ± 56	<0.01
Progesterone(ng/ml)	27.6 ± 13.5	10.2 ± 6.1	<0.01

Table (5): The mean & standard deviation of Prolactin hormone (ng/ml) in normal & aborted groups according to the age distribution:

Age (years)	Normal	Abortion	P value
< 20	45.8 ± 20.6	86.3 ± 58.9	<0.05
20 -30	51 ± 27.1	65.9 ± 42.1	<0.05
31 – 40	38.7 ± 25.4	69.6 ± 58.2	<0.05

Table (6): The Mean & Standard Deviation of Prolactin hormone (ng/ml) in normal & aborted groups according to the gravidity

Gravidity	Abortion	Normal	P value
Prime	89.6 ± 57.6	53.3 ± 25.4	<0.05
Multi	64.3 ± 41.5	50.7 ± 26.3	**0.05**
Grand Multi	38.7 ± 23.6	32.6 ± 18.4	**NS**

Table (7): The mean & standard deviation of Prolactin hormone (ng/ml) in aborted group according to the type of abortion.

Type of abortion	Serum Prolactin (ng/ml)
Threatened	70 ± 49.58
Inevitable	118.8 ± 74.07
Complete	45.64 ± 14.98
Incomplete	74.01 ± 46.67
Missed	62.72 ± 41.79
Recurrent	30.25 ± 7.85
P value	<0.05

Discussion

Spontaneous abortion is a common clinical problem in pregnancy. About 80 % of conceptions are lost during the first trimester, (16). A threatened miscarriage is common, especially in the first trimester, occurring in 14%–21% of all pregnancies, (2, 4). Maternal obesity also has significant detrimental impact on fetal development with an increased risk of isolated and multiple fetal anomalies (13). In the present study there is no obese women in both aborted &

normal pregnant women, also, all studied women are young age (20-29 years). Another study shows that there is increased risk of spontaneous abortion in obese women pregnant after infertility treatment. The underweight women also had a similar risk of spontaneous abortion, (25-26). The relationship between maternal age & abortion was studied by another study that stated that the risk of a spontaneous abortion was 8.9% in women aged 20-24 years and 74.7% in those aged 45 years or more. The other women age group that associated also with high risk of miscarriage is an adolescent (teenager) which means the pregnancy in a woman aged 10-19 years, (27). Hypertension seldom associated with abortion in first trimester. But it may lead to fetal death and premature delivery as it is found that hypertensive disorder of pregnancy form about 5-20% of cases of the antepartum fetal death (4). In the present study all aborted women & control pregnant women at the first trimester are normotensive women. Anemia with hemoglobin levels less than 6 gm/dl is associated with poor pregnancy outcome. Prematurity, spontaneous abortions, low birth weight, and fetal deaths are complications of severe maternal anemia, (28). In the present study, there is no aborted women that had Hb levels less than 9 gm/dl. An Hb concentration of 11 gram/dl in the late first trimester, also Hb concentrations of 10 gram/dl in the 2nd and 3rd trimesters are suggested to be the lower limits for Hb concentration, (28). It has been postulated that some miscarriages are due to corpus luteum deficiency/luteal phase defect where the corpus luteum produces a suboptimal amount of progesterone, resulting in retarded endometrial development. Luteal phase defect has been associated with recurrent miscarriages, infertility. So that progesterone is required for the maintenance of early pregnancy loss, (7), and it is expected to support a potentially deficient corpus luteum and induce relaxation of cramping uterus, (29). Prolactin seems to play an important role in implantation and subsequent placentation in the human endometrium, (15-18), and it is recognized as a crucial signal for the initiation and maintenance of decidualization, (13-17). Therefore, it has been proposed that decidual PRL promotes blood vessel development in the placenta, (16). The results of this study have allowed us to suggest that PRL disorders might be some of the etiologies in the so called "unexplained" habitual abortion, (30-31). In previous study, from a group of 352 women with recurrent spontaneous abortion, we identified 64 patients with a prolactin disorder that was not associated with any other etiologic abnormalities, including ovarian or endocrinologic disturbances such as luteal phase dysfunction, polycystic ovaries, hypersecretion of LH, galactorrhea, or thyroid hormone disorders. Serum prolactin levels during early pregnancy (5-10 weeks of gestation) were significantly higher in patients who miscarried (31.8-55.3 ng/mL) than in patients whose pregnancies were successful (4.6-15.5 ng/mL, $P < 0.01$ or $P < 0.05$), (32). This study in consistence of the present study, which found there is significant increase in serum prolactin in aborted women at first trimester. Recurrent spontaneous abortion is associated with abnormalities in prolactin and androgen secretion during the follicular phase, suggesting an endocrine etiology in this disorder. Reduction of body weight and correction of hyperprolactinaemia and of hyperandrogenism may reduce the rate of miscarriage in a subsequent pregnancy in these women, (33).

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