Association Between Recurrent Miscarriages and Variation of Fertility Hormones in Women Patients of Polycystic Ovary Syndrome

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ABSTRACT

Recurrent miscarriages: This disorder affects 1% of couples trying to conceive, which is defined as the loss of two or more successive pregnancies. Patients miscarry before the 24-week mark in 1-2% of first- and second-trimester pregnancies. Women of reproductive age are frequently affected by the endocrine disorder polycystic ovary syndrome. The study important to know the relationship between recurrent miscarriage in women and polycystic ovary syndrome. The study comprised 90 women, ages 15 to 45, who were split into two groups: 40 women were a healthy control group and 50 patients with polycystic ovarian syndrome and recurrent miscarriages. It used the CL-900i device from Mindray Company in China and ELISA technique to assess the reproductive hormones. The statistical analysis revealed that the women in the sick group had significantly higher levels of prolactin, estrogen, and Inhibin B than the women in the control group. Variations in the levels of a number of hormones, including prolactin, estrogen, and Inhibin B, are suggestive of a higher risk of repeat miscarriages. Patients with PCOS are experiencing more miscarriages; the greatest predictor of a subsequent loss in the future is an earlier miscarriage.

Keywords*:* Recurrent Miscarriages (RM); PCOS; Inhibin B; Estrogen; Prolactin.

1. Introduction

Recurrent miscarriages are most commonly caused by hormonal imbalances. According to specialists, infertility and miscarriage are two examples of reproductive

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failure that share many of the same causes. Those who experience repeated miscarriages are more likely to be infertile [1]. When a female reaches reproductive age, pituitary gland begin to secrete the gonadotropins follicle-stimulating hormone(FSH) and luteinizing hormone(LH), as well as the hormones estrogen and progesterone. These hormones' peak and fall are what control how much are produced and how much are broken down[2]. Women of reproductive age are frequently affected by the endocrine disorder known as PCOS [3]. Menstrual cycle disorders, infertility, late the menopause, cancer of the endometrium, physical issues (central obesity, acne, hair loss, and baldness), psychological issues (depression, stress, and anxiety), metabolic issues (insulin resistance, diabetes type 2, hypertension, and cardiovascular illnesses), are all risks for women with PCOS [4]. From the point of view of biology, women should have children when they are between the ages of eighteen and thirty [5]. Female fertility begins to drop around the age of 30, leading to fewer pregnancies each cycle and finally infertility. One of the aim of this study is to find out whether changes in the levels of these hormones are related to decreased fertility in women as they age [6].

1.1 Symptoms of Recurrent Miscarriage

Recurrent miscarriage has different signs and symptoms. Miscarriage may be asymptomatic or bring back the normal signs and symptoms of pregnancy. Threatening or not, miscarriage is associated with pelvic and abdominal pain, vaginal bleeding, fever, vaginal or cervical secretions, tachycardia, and hypotension. Try to estimate the amount of bleeding because heavier than usual menstruation may indicate a miscarriage. The first day of the most recent menstrual cycle and the results of any prior ultrasounds should be used to determine the gestational age and location of the pregnancy. Signs and symptoms of a miscarriage may be seen in patients who experience heavy bleeding. The final step in identifying the most likely reason for the loss is a pelvic scan [7].

2. Inhibin B

The hormone is a glycoprotein . It has a 32 k Dalton molecular weight. Unbound subunits often have no physiological effects. In a negative feedback loop, Follicle stimulating hormone (FSH) synthesis and release are regulated by the gonadal dimer

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polypeptide hormone Inhibin B As a result, the development of a dimer structure is necessary for its bioactivity. The hypothalamic-pituitary-gonad axis is regulated by a hormone. All through adolescence and childhood[8]. Decades of research have shown that Inhibin B functions physiologically in both male and female reproductive endocrinology applications. It's said to be a sign of a more mature lady. Since it is closely correlated with the number of ovarian follicles, it is sensitive to that quantity [9]. Inhibin B levels rise in women with anorexia nervosa, weight gain, and an increase in fat tissue[10]. Previous research has used inhibitor b to track the aging of the ovaries, detect early ovarian failure or insufficiency, assess ovarian function in cancer survivors, and pinpoint the initial sign of follicle number loss in women [11].

3. LH

A hormone produced from the pituitary gland, activates the corpus luteum and results in ovulation. The ovary secretes progesterone and estrogen throughout the second part of the menstrual cycle[12]. Important gonadotropin in the regulation of the reproductive system is LH. By encouraging the production of sex steroids, LH promotes progesterone release during the luteal phase and initiates oocyte maturation[13]. The hormones LH and FSH, which are normally released on days eight and twelve of a cycle before to ovulation, drive an increase in estradiol (E2) production from the ovaries. Around day 14, progesterone levels increase, whereas estrogen levels rise following ovulation around day 18. the use of hormonal contraception by women. Early in the cycle, progesterone blocks FSH release, delaying the onset of menopause. E2 normally rises, which triggers an increase in LH and prevents ovulation[14]. Pituitary failure may be suggested by disorders including menopause, ovary removal, and premature ovarian syndrome, Nonetheless, decreased gonadal steroid levels and increasing LH and FSH levels might be signs of gonadal failure [15].

4. FSH

Is a kind of gonadotropin hormone that the anterior pituitary gland' basophilic cells manufacture. It is necessary for the management of the reproductive system and the synthesis of gonadal hormones [16]. The ovarian follicle-stimulating hormone (FSH),

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where oocytes or egg cells mature ,the ovaries generate estradiol, promotes the growth and development of the ovarian follicles. Based on FSH, maximum FSH is the most accurate measure of ovarian reserve[17]. FSH promotes the development of follicular cells, the aromatization of androgens to estrogens, and the expression of LH receptors. LH is additionally necessary for the formation of follicles, particularly in the latter phases [18]. FSH flows via a circulation to the gonads, where it activates spermatogenesis in males and follicular development in the females. The physiology of the reproductive systems of both sexes is clearly impacted by FSH[19]. FSH is necessary for development and maturation in females as well as the generation of estradiol. For instance, mono-ovulatory humans. A single kind of egg is produced as a result of FSH's promotion of follicle stimulation, development, selection, and maturity. One developed oocyte is present during the ovulation time[20]. As a result, the FSH levels fluctuate. When the follicular wall ruptures and the cumulus-oocyte complex is liberated, ovulation takes place[21].

5. Estrogen

A steroid hormone that promotes feminine sexual characteristics and is connected to female reproductive systems. In order to have different impacts on the body as a whole, estrogen regulates a range of physiological and pathological processes in both men and women's reproductive system , the immune, endocrine, neurological, skeletal, and cardiovascular systems. As a result, it has been associated with a number of problems, such as polycystic ovarian syndrome, endometriosis, and different malignancies that cause infertility[22]. Estrogen's primary effects include promoting female secondary sex traits and preparing the uterus for ovulation and pregnancy. It also possesses endometrial and breast growth-promoting characteristics in addition to vascular advantages including enhancing blood flow and creating new blood vessels[23]. Although estrogens are typically considered of as feminine hormones, new research shows that they are crucial for male reproduction[24]. In addition, males from birth through adulthood have estrogen receptors found in them[25]. High amounts of estrogen stimulate the pituitary, which then produces unexpectedly high quantities of LH and FSH. The LH surge causes the egg to go through its last stages of maturation, which results in ovulation[26].

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6. Prolactin

The PRL gene in humans produces the protein known as PRL[27]. Prolactin is produced by the human pituitary, myometrium, breast, lymphocytes, leucocytes, and prostate[28]. During pregnancy, high blood levels of prolactin cause the mammary glands to enlarge and prepare to make milk. The process through which the mammary glands make milk is known as lactation. In the latter stages of pregnancy, when progesterone levels start to drop, milk production starts when a suckling trigger is present. Furthermore, the effects of prolactin levels vary depending on age, gender, menstrual cycle stage, and pregnancy. It is necessary to consider the test's circumstances (such as the assay, the patient's condition, etc.) before a prolactin number may be properly interpreted[29]. minimal production of gonadotropins, according to specialists, excessive levels of circulating prolactin that interfere with gonadotropin activity at ovarian level and that affect (positive feedback) at the ovarian level are the two main causes of hypogonadism in women with hyperprolactinemia. Because of the hypothalamus and pituitary's and gonadotropins FSH and LH levels, infertility is caused[30]. Abnormalities associated with behavioral and emotional changes, depression, immunological problems, sexual dysfunction, breast sickness, and reproductive disorders are the most common signs and symptoms of a prolonged increase in prolactin levels in the blood[31].

7. Progesterone

Progesterone is a kind of steroid hormone. This sexual hormone is essential to the wellbeing of the pregnancy. The ovaries employ progesterone, which is generated by luteal phase cells in a developing fetus, as a chemical cue to change the uterine endometrial lining into a highly secretory tissue that can support the fertilized egg [32]. During pregnancy, the placenta, adrenal glands, and ovaries all create progesterone. Additionally, Adipose tissue is where it is kept. Women's pre-ovulatory progesterone levels are low during this time of the menstrual cycle. They increase during ovulation and hold their high levels throughout the luteal phase. Progesterone levels typically range from less than 2ng/ml before ovulation to more than 5ng/ml after ovulation seven days before menstruation[33]. In ovulation, the egg is expelled from the follicle while being encircled by cumulus cells.

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The luteal phase, which typically lasts 14 days after ovulation with minimal variation, is caused by the ovary's surviving follicular cells becoming luteinized and producing progesterone. LH is still being produced, which ensures a steady supply of progesterone that helps women get ready for pregnancy and maintains the health of their endometriums. Progesterone are highest during the (luteal phase) of a cycle. Additionally, the high levels of progesterone prevent any further ovarian follicular expansion during that cycle by limiting the release of FSH and LH[34]. Although it helps maintain the endometrium and hence the pregnancy, progesterone is essential before and throughout pregnancy[35].

8. Subject and Material

At the Kerbala City Gynecological and Obstetric Teaching Hospital and the female outpatient clinics, a case-control research was carried out. From October 2021 to September 2022, all samples were taken. A total of 90 Iraqi women between the ages of 15 and 45 who were not pregnant participated in the research. Group 1 was made up of 40 women who had at least one child but had never experienced a miscarriage. They were free of any indications or symptoms of illness, and their ages were matched to those of women who experienced repeated miscarriages. 50 women in Group 2 who had polycystic ovarian syndrome and at least two recurrent miscarriages. Women who underwent a physical examination and completed a brief questionnaire including their height, weight, number of miscarriages, and length of pregnancy. The samples were allowed to remain at room temperature for 15 minutes before the serum was separated and maintained at -20o C unless it was immediately needed. Inhibin B, LH, FSH, estrogen, prolactin, and progesterone tests required blood samples to be taken from non-pregnant women. 5 ml of blood were drawn with a medical syringe and then placed in gelatin tubes.

9. Results

Variables were compared using independent T-test statistics between study groups, and the findings were reported as mean, SD, and extraction P-value to indicate the difference in variation. Comparing the levels of the fertility hormones Inhibin B, LH, FSH, prolactin, progesterone, and estrogen in the serum between women who have experienced recurrent miscarriages and healthy subjects revealed that Inhibin B levels were

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significantly decreased in patients (P=0.05), FSH levels were insignificantly increased (P=0.05), LH levels were insignificantly increased (P=0.05), prolactin levels were significantly increased in patients (P=0.05), When compared to the control group, the progesterone level in patient women was not considerably higher (P=0.05), while the estrogen level was significantly higher (P=0.05) in patient women, according to the "table" 1.

Table 1. The concentration of Inhibin B, LH, FSH, estrogen, progesterone and prolactin of patients and control group.

parameters	subject	Mean± SD	P value
Age (Years)	patient Control	67.16 ± 12.64 64.32 ± 12.38	0.05
BMI (kg/m^2)	patient Control	25.94 ± 4.60 25.70 ± 4.85	0.05
INHIBIN B (pg/ml)	patient Control	115.56 ± 10.93 133.64 ±10.00	0.05
FSH (mlU/ml)	patient Control	7.01 ± 1.98 6.14 ± 1.64	0.05
LH (mlU/ml)	patient Control	7.52± 2.12 5.71 ±1.85	0.05
Prolactin(mlU/ml)	patient Control	15.02 ± 8.62 12.02 ± 6.58	0.05
Progesterone(ng/ml)	patient Control	0.54 ± 0.18 0.53 ± 0.17	0.05
Estrogens (pg/ml)	patient Control	51.82± 18.15 37.92 ± 13.45	0.05

BMI: Body Mass Index ; FSH: Follicle stimulating hormone ; LH: Luteinizing hormone ; SD: Standard deviation ; P-value: Probability level of statistical ; N.S: t-test p- value ≥ 0.05; No. of patients group=50; No. of control group=40

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9.1 The levels of the hormones Inhibin B, estrogen, and LH during the miscarriage period in patients' women

In this study, measurements of the concentrations of estrogen, LH, and Inhibin B in patients with miscarriage length revealed that these hormone levels were greater in one month compared to two and three months, as shown in figures (1,2 and3).

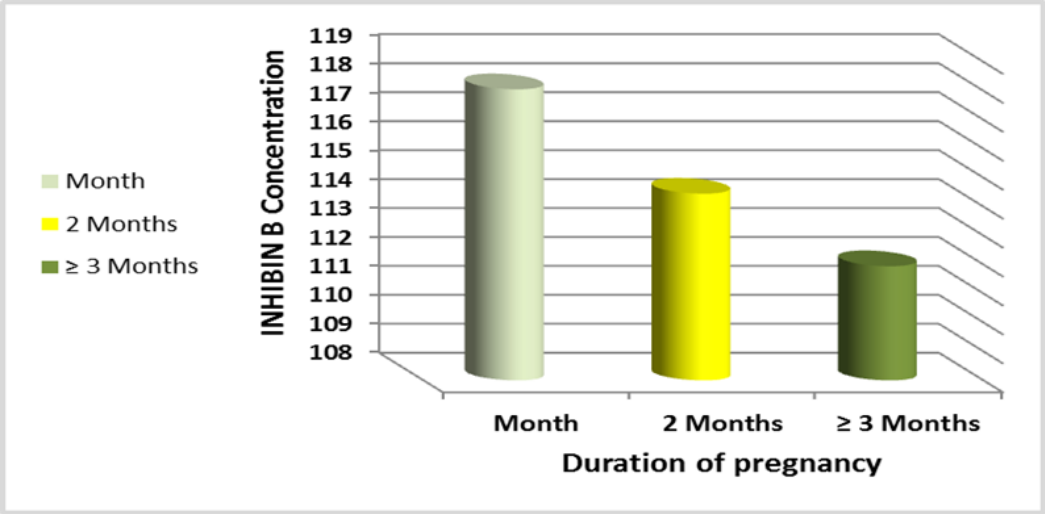

Figure 1. The relation of duration of miscarriage with Inhibin B concentration.

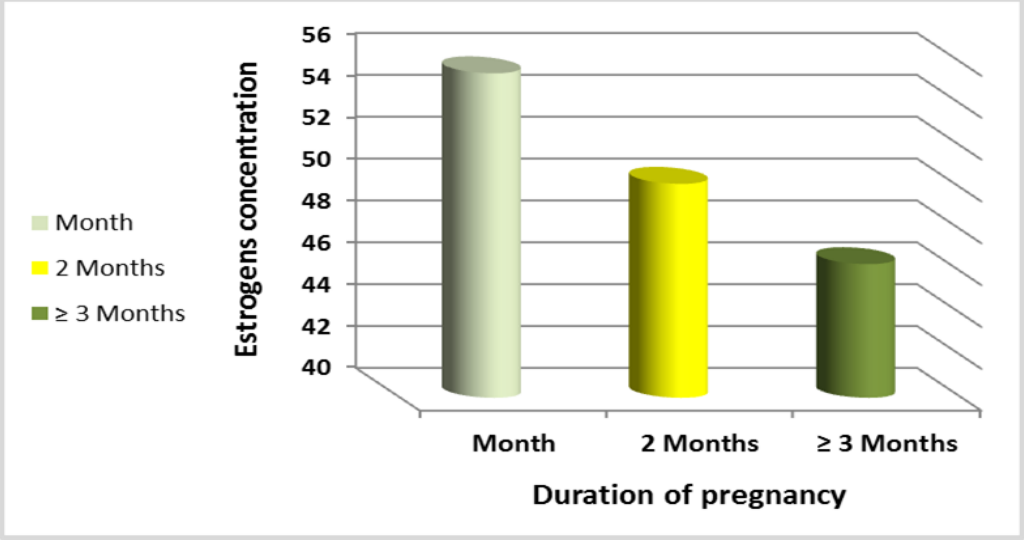

Figure 2. The relation of duration of miscarriage with estrogen concentration.

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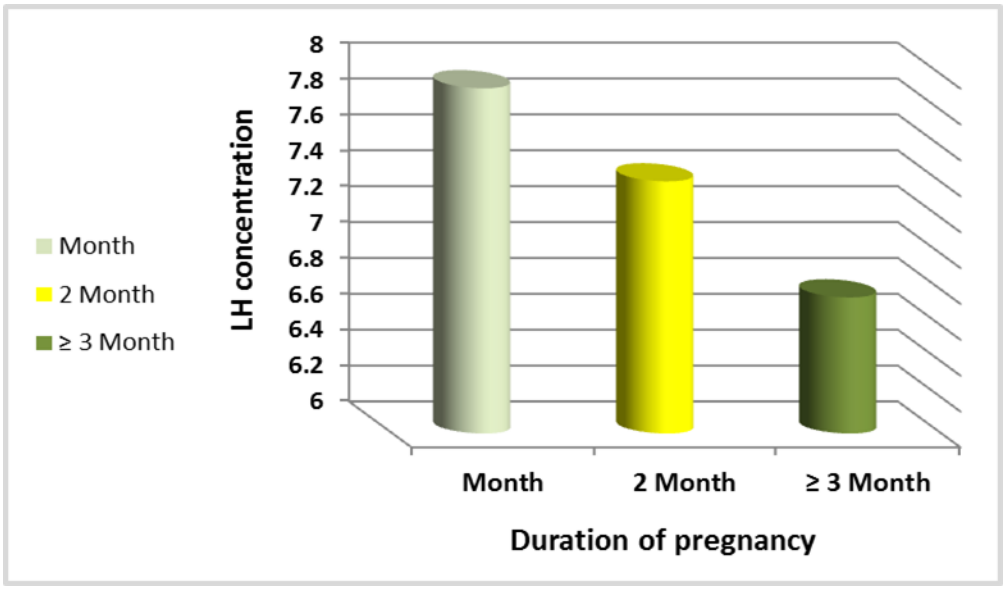

Figure 3. The relation of duration of miscarriage with LH concentration.

9.2 The levels of the hormones prolactin, progesterone, and FSH during the miscarriage period in patients' women

More miscarriages occur in the third or later stage of pregnancy than in the first and second months after embryo age, according to the assessment of these hormones with miscarriage length, as shown in figures(4,5and6).

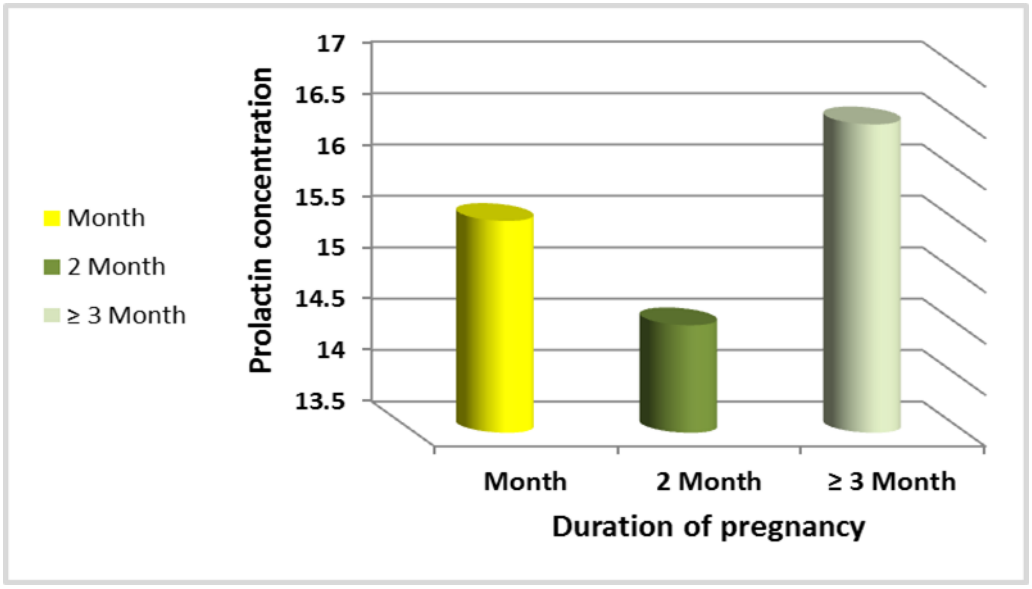

Figure 4. The relation of duration of miscarriage with prolactin concentration.

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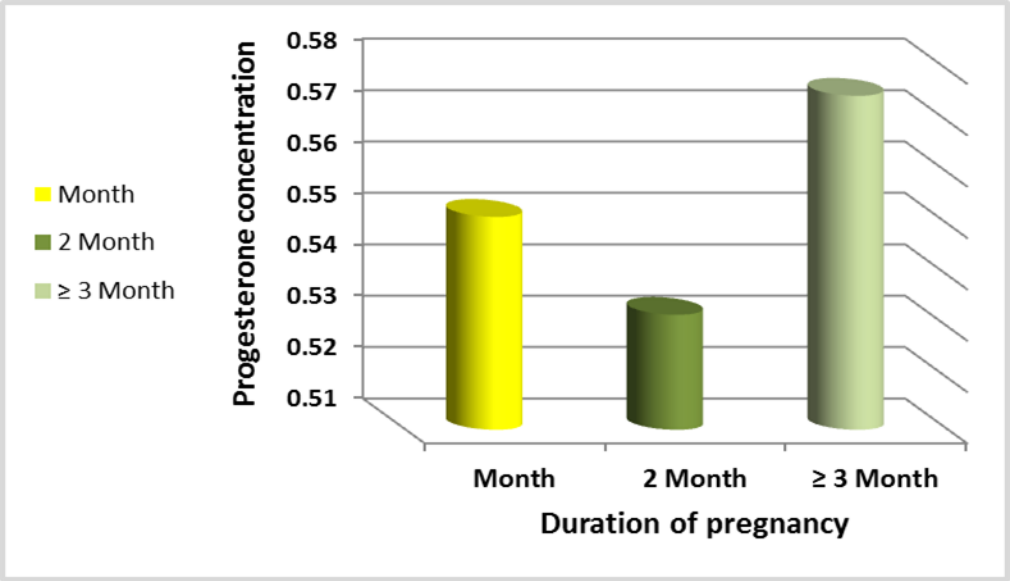

Figure 5. The relation of duration of miscarriage with progesterone concentration.

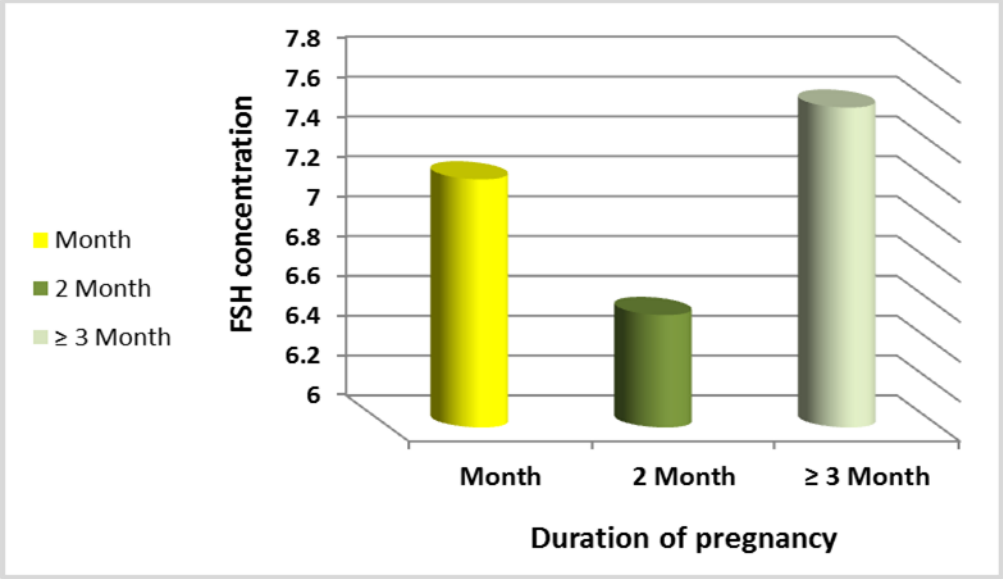

Figure 6. The relation of duration of miscarriage with FSH concentration.

10. Discussion

In women with PCOS and the control group, hormone findings showed that levels of Inhibin B were lowered, while levels of FSH, LH, estrogen, prolactin, and progesterone

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were raised. Low pregnancy rates, poor ovulation, and a higher chance of miscarriage have all been associated with low Inhibin B levels. Research suggests The relationship between Inhibin B concentration and follicular function and oocyte number raises the possibility that Inhibin B cell product contributes to follicular growth[36]. Because Inhibin B levels fall before blood FSH levels increase, it is a more accurate gauge of ovarian age than FSH. Patients utilizing progesterone to treat polycystic ovarian syndrome had reduced Inhibin B levels[37]. Studies have indicated that individuals with polycystic ovarian syndrome had higher concentrations of Inhibin B [38]. However, some have shown that it reduces[39] . Patients with polycystic ovarian disease do not ovulate because of a high LH/FSH ratio. Higher serum LH levels and the LH:FSH ratio are typical in PCOS women. According to one study, the LH/FSH ratio varies at least as much in healthy women as it does in people with clinical PCOS[40]. During the follicular and luteal stages of menstruation show a little rise in blood prolactin levels in 30% of PCOS patients. Research suggests that a rise in blood prolactin levels may cause ovarian follicles and ovulation to decline. Early research revealed that patients with polycystic ovaries had higher blood levels of prolactin. Recent investigations have discovered a less frequent connection between these illnesses. These research employed repeated blood samples to rule out transient prolactin surges [41]. Lack of luteal phase progesterone production and activity is a major contributor to infertility and spontaneous abortion; however, the source of progesterone shortage in PCOS patients during the luteal phase remains unclear. Vaginal progesterone treatment may be helpful for women who have a history of miscarriage and are suffering early pregnancy bleeding. An increased likelihood of live births was associated with the use of 400 mg of vaginally administered micronized progesterone twice day[42]. During pregnancy, the placenta also secretes significant quantities of estrogens. Women with polycystic ovarian syndrome (PCOS) may experience high estrogen levels. A hormonal imbalance that can lead to irregular periods, unwanted hair growth, and acne is what this illness is known for. A hormonal imbalance is the root cause of the estrogen dominance seen in PCOS-afflicted women. Environmental factors may also have an impact on the result[43]. One to five percent of pregnancies have early miscarriage, which is defined as pregnancy loss that occurs within the first three months of pregnancy (less than 12 weeks gestation). The second trimester (12–24 weeks) is the most prevalent time for late

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miscarriage, which occurs 1-2% of pregnancies. A parallel investigation revealed that first trimester failure occurs more frequently than other months[44]. Women with PCOS are three times more likely to miscarry in the first trimester of pregnancy than are women without PCOS. Threatening miscarriages brought on by cultural and environmental factors have become more prevalent in recent years. Progesterone, estrogen, and prolactin are sex hormones that govern communication between the mother and the embryo during the first trimester. Currently, it is impossible to anticipate and assess first-trimester pregnancies with bleeding without the use of reliable indications. Blood progesterone levels are the main markers used to detect and assess the prognosis in women experiencing an abortion risk. Occasionally, estrogen levels are also applied. The most typical therapies for threatened miscarriage are bed rest, luteal support, and a combination of estrogen and progesterone supplements[45].

11.Conclusions

Recurrent miscarriages are more common in pregnant women than in non-pregnant women due to differences in the levels of certain hormones, such as prolactin, progesterone, LH, FSH, estrogen, and Inhibin B. Women of reproductive age in all age groups (15–45) have been seen to experience recurrent miscarriages and decreasing levels of Inhibin B. In order to determine the chance of a miscarriage, these characteristics are evaluated as part of their adoption.

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