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The effect of ACTIVIN A hormone levels in women who suffer from recurrent miscarriages with polycystic ovary syndrome

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ABSTRACT

Introduction: During pregnancy, the placenta is the primary source of the gonadal protein ACTIVIN A in the mother's bloodstream. From mid-pregnancy until close to term, the mother's blood levels of ACTIVIN A rise. Placental malfunction complicates pregnancies, as evidenced by intrauterine foetal growth restriction and significantly higher levels of ACTIVIN A in the mother's blood compared to a normal pregnancy. Experts believe that the elevated blood levels of ACTIVIN A stem from heightened placental synthesis.

OBJECTIVE: This study aimed to determine the levels of the ACTIVIN A hormone in the blood of women with PCOS who experience recurrent miscarriages, compare those levels to those of the control group, and confirm the association between the hormone and maternal age and obesity.

Method: We included ninety women between the ages of fifteen and forty-five in a case-control study; fifty of them had a diagnosis of polycystic ovarian syndrome, while the remaining forty belonged to the healthy control group. The USA-based BioTek Company collected samples between October 2021 and March 2022, using its absorbance ELISA microplate reader and ELISA microplate washer to assess the samples' levels of ACTIVIN A. We calculated the concentration of ACTIVIN A by dividing the weight by the height in square meters.

RESULTS: When compared to the control group, the sick women's levels of ACTIVIN A considerably decreased (P = 0.05). Furthermore, compared to polycystic ovary syndrome patients, the control group had the highest level of AVTIVIN. The concentration was measured based on the body mass index.

CONCLUSION: Patients with polycystic ovarian syndrome had lower levels of ACTIVIN A. Obese women formed a greater percentage of the patients' BMI. Researchers discovered a high amount of ACTIVIN A in the first month of pregnancy. Furthermore, research has linked this hormone to an increase in the frequency of recurrent miscarriages, with the hormone concentration being higher on the day of the most recent miscarriage, which occurs between one and four months, than it is over the longest period of time.

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1. Introduction

Researchers have linked a 25 K Dalton homo-dimer known as ACTIVIN A to several biological activities, including the release of FSH and the development of mesoderm, neural cells, follicular cells, and red blood cells [1]. The term miscarriage refers to the loss of a pregnancy before the embryo becomes viable. Therefore, the term encompasses all miscarriages from conception to 24 weeks of pregnancy [2]. Depending on the type, there are different signs and symptoms of spontaneous miscarriage. Natural pregnancy symptoms and indicators may reappear after a miscarriage, or they may not show any symptoms at all. Abdominal-pelvic cramping, vaginal bleeding, fever, vaginal or cervical secretions, tachycardia, and hypotension are all associated with miscarriages, whether or not they are life-threatening. Estimate the amount of bleeding, as a greater than usual amount during a menstrual cycle may indicate a miscarriage. Patients experiencing significant bleeding may display symptoms and indicators of a miscarriage; one should use the last day of the menstrual cycle and results from previous ultrasounds to ascertain the gestational age and location of the pregnancy. Finally, a pelvic examination establishes the cause of a possible miscarriage [3]. Undoubtedly, obesity is well acknowledged to independently elevate the likelihood of miscarriage. The incidence of pregnancy and abortion is greatly influenced by obesity before conception [4]. An abnormal architectural configuration of the uterus heightens the probability of spontaneous abortion. Uterine septum and uterine fibroids have the ability to modify the typical structure and intra-uterine environment of the uterine cavity, which may result in difficulties. Enhanced resistance to blood flow, decreased blood flow in the endometrium, and restricted room for embryo implantation have adverse effects on the development, growth, and implantation of embryos. This disorder, classified as a kind of endometriosis, heightens the likelihood of complications during embryonic development. The mechanism by which it does this is by inducing inflammation, modifying the uterine wall, and generating diverse hormonal effects that eventually lead to death. Furthermore, research have shown that women diagnosed with polycystic ovarian syndrome may have a higher likelihood of undergoing spontaneous abortions [5]. Considering its many problems, abortion is not only a financially burdensome health concern for society, but also a social issue within the community, since it eventually jeopardizes people's well-being [6]. The findings of many research have shown that women's attitudes undergo changes six weeks after an abortion, and that the termination of pregnancy has positive psychological impacts on women. Distresses associated with abortion may manifest in a woman's personal life via several means, including feelings of remorse and emptiness. Moreover, women who have had spontaneous abortions have a dual risk of experiencing severe depression. Typically, this begins during the first week after an abortion. Among women, it is more pronounced [7]. Recurrent miscarriage is associated with femininity; thus, women who experience it are more likely than men to confront social and familial challenges. Frequent miscarriages might result in remarriage, separation from your partner, divorce, family threats, and psychological distress [8]. Polycystic ovary syndrome-affected women are more likely to experience metabolic problems (insulin resistance, diabetes type 2, hypertension, and cardiovascular diseases), physical problems (central obesity, acne, hair loss, and baldness], psychological problems (depression, stress, and anxiety), and reproductive problems (menstrual cycle disorders, failure to ovulate, late menopause, endometrial cancer, and infertility) [9]. The majority of people with polycystic ovary syndrome PCOS only exhibit one or two clinical symptoms. Menstrual disorders, which often start at or shortly after menarche and can manifest as hypomenorrhea, amenorrhoea, or polymenorrhea, are the most common clinical

findings until the menstrual cycle is regular [10]. The period of menstruation is a natural occurrence that denotes a woman's fertile years. It indicates menstruation and reproduction, as well as the importance of women's health. At this stage, most women are experiencing pain. Hormonal variations might cause you to have a range of symptoms [11]. Hormonal fluctuations associated with menstrual disorders, such as elevated or decreased hormone concentrations, have profound effects on the body [12]. This study aimed to determine the levels of the ACTIVIN A hormone in the blood of women with PCOS who experience recurrent miscarriages, compare those levels to those of the control group, and confirm the association between the hormone and maternal age and obesity

2. Method

This research, done by the chemistry department of the University of Karbala College of Education for Pure Science, included 50 patients diagnosed with PCOS and experiencing recurrent miscarriages, as well as 40 otherwise healthy women (controls) aged between 15 and 45. The case The cases between October 2021 and March 2022 were supplied by the Gynaecological and Obstetric Teaching Hospital. 2003 Rotterdam criteria for diagnosing Polycystic Ovary Syndrome (PCOS) in women. The criteria were clinical manifestations of hyperandrogenism, ultrasonography, biochemical markers, and the presence of polycystic ovaries prior to ovulation. Hematological sample Blood samples are collected from non-pregnant individuals at outpatient clinics and the Gynaecological and Obstetric Teaching Hospital for the purpose of conducting fertility hormone (ACTIVIN A) testing. A volume of five millilitres of blood was extracted using a 5-millilitre medical syringe. d Following that, we put the blood into gelatine tubes devoid of anticoagulant components, since gelatine aids in the segregation of serum during centrifugation. The specimens were left at ambient temperature for fifteen minutes before being subjected to centrifugation at a speed of 2500 rpm for ten minutes to separate the serum. The resulting serum was then kept at -20 °C until it was needed immediately.

3. Results and Discussion

The study's data were examined using the Statistical Package for the Statistical Analysis System [SAS] 2012 application. It was intended to be used for substantial contrasts and comparisons. When the mean ±SD (standard deviation) was shown and the p-value was less than 0.05, it was deemed significant. Statistics from independent T-tests were used to compare parameters between the patient and control groups.

Table 1: Comparison of ACTIVIN A concentration between patients women and control group for age (15-45) years

parameters	*subject*	*Mean± SD*	*P value*
Age [Years]	Control	64.32 ± 12.38	*0.05*
	patients	67.16 ± 12.64	
BMI	Control	25.70 ± 4.85	*0.01*
	patients	25.94 ± 4.60	

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ACTIVIN A	Control	262.52 ± 8.54	*0.05*
	patients	240.57 ± 10.60	

SD- standard deviation, BMI -Body Mass Index, NS- t-test p- value ≥ 0.05, No. of patients group=50 , No. of control group=40

Patients aged 15–45 had an average ACTIVIN A level of 240.57 ± 10.60pg/ml, according to the provided data, while the control group had 262.52 ± 8.54pg/ml. When comparing the sick group to the control group, ACTIVIN A levels were significantly lower in the patient group (P=0.05). Despite having a comparable body mass index to the control group, the ill women were much older.

Table 2: Comparison of ACTIVIN A concentration between patients and control for age (15-29) years

parameters	*subject*	*Mean± SD*	*P Value*
Age [Years]	**Control [15-29]**	**60.95 ± 12.61**	***0.05***
	Patients [15-29]	**61.95 ± 10.76**	
BMI (kg/m^2]	**Control [15-29]**	**24.51 ± 4.80**	***0.01***
	Patients [15-29]	**23.65 ± 3.99**	
ACTIVIN A (pg/ml)	**Control [15-29]**	**259.60 ± 8.42**	***0.01***
	Patients [15-29]	**240.55 ± 15.46**	

SD-standard deviation, BMI-Body Mass Index, NS- t-test p- value ≥ 05, No.of patients group=50, No. of control group=40

The data given indicates that the mean ACTIVIN A levels were substantially lower in the patient group [P=0.01] when compared to the control group. The mean levels in the patients aged 15-29 years were 240.55±15.46pg/ml, while the control group's levels were 259.60 ± 8.42pg/ml. When compared to the control group, the age measurement of the patient women increased slightly, while the patient women's body mass index level reduced somewhat.

Table 3: Comparison of ACTIVIN A concentration between patients and control for age (30-45) years

parameters	*subject*	*Mean± SD*	*P Value*

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Age(Years)	**Control (30-45)**	**68.44 ± 11.06**	***0.03***
	Patients (30-45)	**76.05± 9.83**	
BMI (kg/m^2)	**Control (30-45)**	**27.15 ± 4.63**	***0.01***
	Patients (30-45)	**29.36± 3.13**	
ACTIVIN A (pg/ml)	**Control (30-45)**	**266.09± 7.42**	***0.01***
	Patients (30-45)	**240.62 ± 13.6**	

SD-standard deviation, BMI- Body Mass Index, NS-t-test p- value ≥ 0.05, No. of patients group=50 , No. of control group=40

The mean ACTIVIN A levels in patients (30–45 years old) were found to be 240.62± 13.6 pg/ml, while the control group's levels were 266.09 ± 7.42 pg/ml. The data given indicates a significant drop in the patient group [P=0.01] when compared to the control group. When comparing the sick group to the control group, the patient group's body mass index level (P=0.01)and age level (P=0.03) both considerably rose.

Effect of BMI on ACTIVIN A concentration in patients and control group: - When

compared to the women in the patient group, the study discovered that the control group's levels of ACTIVIN A concentration were greatest in terms of Body Mass Index (BMI), regardless of whether the women were obese, overweight, or normal weight, as seen in Figure 1.

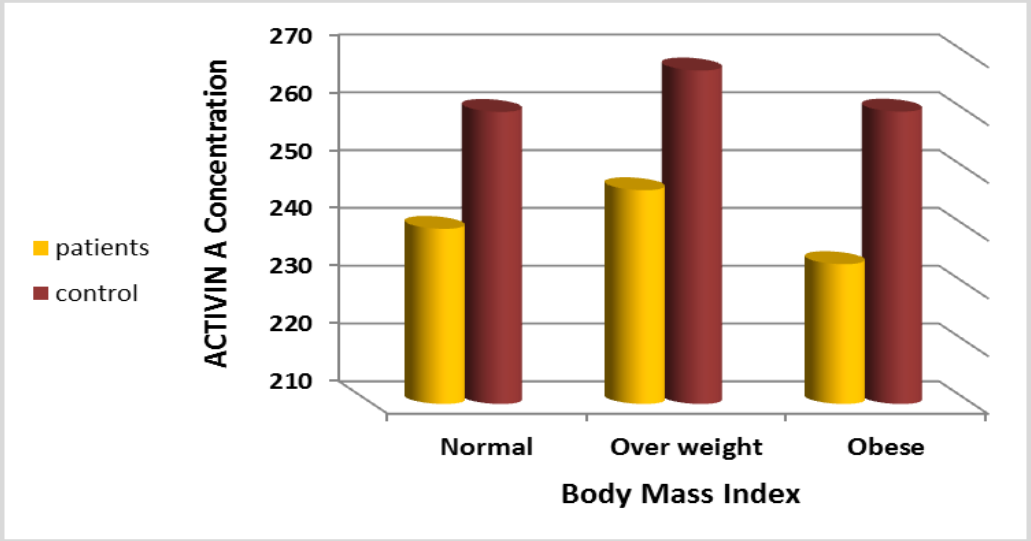

Figure 1: Levels of BMI with ACTIVIN A concentration in patients and control group.

Effect of the duration of pregnancy on ACTIVIN A level in patients group:- According to the study's findings, patients' levels of ACTIVIN A concentration increased with the length of their miscarriages one month was associated with a higher rate of miscarriages than three or two months, as seen in figure 2.

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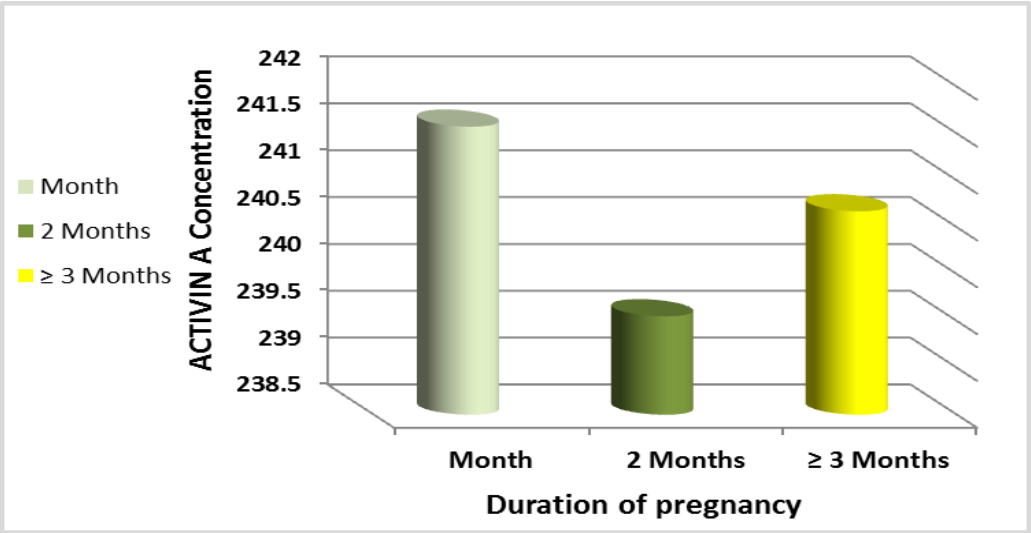

Figure 2: The relation of duration of pregnancy with ACTIVIN A concentration.

Influence of number of miscarriages on ACTIVIN A concentration in patients women:- According to the results of this study, women who experience two recurrent miscarriages are more likely than other women to have three or more miscarriages, which also reveal a correlation between the concentration of the hormone ACTIVIN A and the number of miscarriages among the patient women, as seen in Figure 3.

Influence of last miscarriages date on ACTIVIN A concentration:- The study discovered that, in comparison to the second group [5–9 months] and third group (beyond 9 months–2 years), the level of concentration of ACTIVIN A hormone was larger percentage in the first group [1-4 months] for the last miscarriage date for patient women, as seen in Figure 4.

3.1. DISCUSSION

Comparisons of hormone levels between the control group and those with PCOS revealed reduced levels of ACTIVIN A. Pregnant women have elevated blood concentrations of ACTIVIN A compared to non-pregnant women, and these concentrations further rise throughout the duration of the pregnancy until about week 28 [13]. The use of serum ACTIVIN A as a prognostic indicator of pregnancy failure is a subject of contention among scholars. A contention exists that ACTIVIN A levels have the potential to detect pregnant women who are at risk of unnoticed miscarriages [14]. Quantification of the ACTIVIN A hormone level is essential for managing early pregnancy complications during the first trimester in women experiencing bleeding that heightens the risk of miscarriage for the embryo [15]. A decrease in ACTIVIN A concentration or effective potency might lead to symptoms like those of PCOS [16]. Based on the results, the average levels of ACTIVIN A in patients aged 15-45 were 240.57 ± 10.60 pg/ml, whereas the control group had 262.52 ± 8.54 pg/ml. The sick group exhibited a statistically significant decrease in ACTIVIN A levels (P = 0.05) in comparison to the control group. In contrast to the control group, the average age of the ill women was much greater, and their body mass index level was almost same, as shown in Table W. The presence of ACTIVIN A in the bloodstream during pregnancy is controversial due to the unclear biological role of these proteins [17]. The origin of serum ACTIVIN A in women is unidentified; the peptide is produced by ovarian cells responding to FSH stimulation [18].

According to the provided data suggests that the patient group's mean ACTIVIN A levels were significantly lower (P = 0.01) than those of the control group. The mean levels in the patients aged 15–29 years were 240.55±15.46 pg/ml, while the control group's levels were 259.60 ± 8.42 pg/ml. Table 2 shows that the patient women's age measurement increased slightly compared to the control group, while their body mass index level decreased slightly. Patients with PCOS had significantly lower serum ACTIVIN A levels than controls [19] discovered in another investigation that PCOS patients had reduced levels of ACTIVIN A [20]. According to [21] serum ACTIVIN A levels in patients with miscarriages had varying outcomes, with levels significantly lower in patients who were women.

According to the mean ACTIVIN A levels in patients (30–45 years old), they were found to be 240.62± 13.6 pg/ml, whereas the control group's levels were 266.09 ± 7.42 pg/ml. The provided data shows a significant decrease in the patient group's ACTIVIN A levels (P = 0.01) in comparison to the control group. When comparing the sick group to the control group, Table 3 shows a significant increase in the patient group's body mass index level (P = 0.01) and age level [P = 0.03]. PCOS may result from hormone levels that are higher or lower than usual, which can have an impact on the ovarian system. Therefore, among women diagnosed with health problems including obesity, stroke, and other disorders, age-related health difficulties may increase the likelihood of PCOS, and PCOS may worsen these conditions. Hence, early screening and treatment of PCOS patients is necessary to reduce health risks to women. Our study found that in two age groups, 15–29 and 30-45 years, ACTIVIN A levels were greater in the control group compared to PCOS-affected women [22]. Correspondingly, a glycoprotein that binds to ACTIVIN A and blocks its function was shown to be present at lower blood levels in PCOS individuals [23]. We divided the BMI-assigned individuals into three groups. We assigned normal weight individuals (18.5-24.9 kg/m2), overweight individuals (25-29.9 kg/m2), and obese individuals (>30 kg/m2) to groups A and B. According to the results of the current investigation, the control group's levels of ACTIVIN

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A concentration and BMI were greater than those of the PCOS patient women. Figure 1 shows that when measuring ACTIVIN A concentration, the control group's BMI was higher in the overweight category compared to the normal and obese categories. According to a study that supports ours, women with PCOS had lower body mass indices of ACTIVIN A than those without the condition [24]. In actuality, not all PCOS-affected women are obese [25]. Since PCOS directly interferes with a patient's ability to reproduce, it is imperative to diagnose the condition because it may imply metabolic issues, potential cardiovascular issues, and other issues [26].

The present study discovered a correlation between the length of the miscarriage and the biochemical parameters of the women who experienced it. These characteristics affected the levels of reproductive hormones at one, two, and three months or more after the miscarriage ended. According to the study's results, the concentration of ACTIVIN A in patients' blood was shown to correlate with the duration of their miscarriage. Figure 2shows that the incidence of miscarriages was highest at one month, followed by three and two months. One in five pregnancies ends in an early miscarriage, which is defined as the loss of a pregnancy that happens within the first three months of the pregnancy, namely, before twelve weeks of gestation. One to two percent of pregnancies result in late miscarriages, which are rare and occur in the second trimester [12–24] weeks [27]. First trimester failure is more prevalent than later months, according to matched research [28]. In the first trimester of pregnancy, women with polycystic ovarian syndrome had a threefold higher risk of miscarrying compared to those without PCOS [29]. Low blood oxygen levels impact the embryo placenta, which increases the placenta's release of ACTIVIN A in the latter stages of pregnancy. Up until delivery, the ACTIVIN-A hormone keeps rising during pregnancy. This hormone may serve as an indirect indicator of a lack of internal uterine oxygen. Women who have miscarriage-risking pregnancy-related bleeding measure the level of ACTIVIN A at the beginning of pregnancy to identify deficiencies in cell function and control early pregnancy requirements in the first trimester. ACTIVIN A regulates cell division and increases the release of follicle-stimulating hormone [30].

For this investigation, we used the patients' reported history of miscarriages to classify them into two, three, or more categories. After that, they analyzed the correlation between the hormone variations and the patients' fertility hormone levels. Furthermore, compared to women who have three or more miscarriages, the likelihood of this happening increases for women who suffer two repeated losses (figure [3]). The most significant risk factor for miscarriage, according to a large body of data on recurrent miscarriage, is a recent spontaneous loss. The first pregnancy result is the strongest indicator of future spontaneous miscarriage, which in turn affects all subsequent pregnancies [31]. The relationship between PCOS and repeated miscarriages has been the subject of several studies in the past few years. Studies have observed a higher incidence of PCOS in women experiencing repeated miscarriages [32]. [33] found a link between obesity and a higher number and risk of recurrent miscarriages in PCOS patients. Researchers have discovered that the level of ACTIVIN A during the first two weeks of pregnancy can predict the outcome of the pregnancy. Pregnancies destined to miscarry appear to have a lower concentration of ACTIVIN A compared to those that result in delivery [34].

The study involved dividing the female patient group into three groups based on the date of their most recent miscarriage: the first group had their last miscarriage within the last four months, the second group within the last five to nine months, and the third group beyond the last nine months to two years. We also compared the concentration of fertility hormones across the groups to

understand their impact on the hormone level. As illustrated in figure 4, the study found that, compared to the second group (5–9 months) and the third group beyond 9 months–2 years, the first group [1-4 months] had a higher level of ACTIVIN A hormone concentration for the latest miscarriage date among the patient women. On the other hand, prolonging the gestational age following a loss usually improves the success of the next pregnancy. A World Health Organisation (WHO) expert panel on birth spacing advises delaying the next pregnancy for at least six months after a miscarriage to improve outcomes. A single large Latin American study, which found a correlation between a greater risk of preterm delivery and miscarriage-pregnancy lengths of less than six months, derived this guidance. It should come as no surprise that maternal serum ACTIVIN A levels rapidly drop after pregnancy loss, sometimes even before clinical symptoms appear [35]. However, a separate group's subsequent study found these markers ineffective in predicting an impending miscarriage in women without any symptoms [36, 37, 38].

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