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THE ROLE OF THROMBIN IN PRETERM LABOUR IN TIKRIT CITY

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Abstract

The background material states that a wide number of markers were examined because preterm birth remains a significant treatment problem.The **aim** of the present study is to examine whether the plasma levels of the thrombin-antithrombin (TAT) complex have any clinical utility in the assessment of the risk of preterm birth in women diagnosed with preterm labor. The **study was** conducted at Tikrit Teaching Hospital and comprised 85 pregnant women who attended the hospital between 24 and 34 and a half weeks of their pregnancy. The study design was case–control. Overall, sixty of the pregnant women identified with PTL were hospitalized and closely watched for any issues that may have

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occurred during their pregnancy. The study control group comprised twenty-five women with no history of preterm labor, who were recruited from the outpatient clinic and had a gestational age of between twenty-four and thirty-four plus six weeks. The time-to-finish value was calculated by ELISA.

RESULT Of the 85 pregnant women participating in the trial, 60 were diagnosed with threatened postterm labor. Among the 60 women, 26 experienced premature delivery within three weeks of admission and 34 delivered sometime after admission.The level of TAT in patients with preterm labor and delivery before the predicted period is significantly higher. Delivery If the TAT level exceeds 120, delivery occurs within three weeks. Delivery occurs within three weeks if the TAT level exceeds 120. Specificity: 98%, Accuracy: 99%, Sensitivity: 100%. **CONCLUSION:**The TAT test was found to be sensitive and specific. Women with symptoms of preterm delivery who subsequently delivered prematurely, especially those delivering within three weeks, had significantly higher TAT levels.

Keywords: Thrombin, Preterm Labour, hemorrhage, placental, low birth weight.

Introduction

Definition:-Preterm labor is the increasing effacement and dilation of the cervix before the predicted date of delivery, usually between 24 and 37 weeks of gestation (1). Mildly preterm labor is defined as 32+0 to 36+6 weeks of gestation (incidence 5.5%), moderately preterm labor as 28+0 to 32+6 weeks of gestation (incidence 0.7%), and severely preterm birth as 24+0 to 27+6 weeks of gestation (incidence 0.4%). This division is necessary for reasons of etiology, outcome, and risk of recurrence (1, 2, 3). The weight of preterm babies is classified into three: low birth weight (1.5-2.5 kg), very low birth weight (1-1.5 kg), and extremely low birth weight (<1 kg) (4, 5). Preterm labor occurs in 7–12% of the developed world (1). Assisted reproduction has been associated with a higher propensity for

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obstetric intervention and a small but consistent increase in the occurrence of premature labor. The incidence of preterm labor <32 weeks of gestation has been stable at 1-2%. A quarter of premature births are elective, most of them due to pre-eclampsia, intra-uterine growth restriction, or maternal disease, while the remainder are due to problems of labor and delivery. Women in their 20s have the lowest prevalence, but teenagers and women in their 30s are at increased risk (1, 3).The "threshold of viability" is the stage in the pregnancy where the baby has a 50% probability of surviving. Over the past 40 years, neonatal intensive care units (NICUs) have made significant advances, cutting the viability span in half, to roughly 24 weeks (7).

The term 'miscarriage' includes deliveries before 23 weeks, and the 'grey zone of viability' refers to the few situations in which an infant survives after birth (8).

The effects of premature birth on the newborn:

For example, at 23 weeks gestation, the death rate for premature labor is 90%, and the morbidity and expense involved are substantially greater. By week 34, that had reduced to 2 percent. There is a high risk of both immediate and delayed morbidity, even in surviving infants (9, 10). ...

1- Short-term morbidity:

These include respiratory distress syndrome, retinopathy of prematurity, periventricular leukomalacia, patent ductus arteriosus, intraventricular hemorrhage, sepsis, and necrotizing enterocolitis (9).

2-Long-term morbidity:

A. Paralysis of the brain.

The newborn and fetal brains are most susceptible to injury between twenty-two and thirty-two weeks after conception. Boys have a greater rate of fetal and

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neonatal mortality (9), and those born before 28 weeks or weighing less than 1 kilogram are at increased risk of neurological and motor impairments later in life.
B. B. Hearing impairment. of hearing.
C. Intellectual disability, which is learning difficulties and poor academic performance.
D. Failure of visual-motor synchronization.
E. Increasing impairment in late childhood.
F. Abnormal airway function has been described in premature infants with respiratory distress syndrome [12, 13].

Etiology of Preterm Labour:-

Three reasons why babies are born too early have been found:
1. The cervical pathway and infection.
2. The course of the placental vessels.
3.The manner of tension and compression.

All these factors contribute to the identification of high-risk patients and the development of effective interventions (14, 15).

Pathogenesis

1. Idiopathic: - In 60-70% of preterm infants, no etiology is established (16).
2. The hypothalamic-pituitary-adrenal axis is activated earlier than it should be.
3. An infection ..

Uterine infections are strongly associated with the onset of spontaneous labor. Uterine infections can initiate a cascade of biochemical processes that lead to cervical ripening and uterine contractions. The most consistent association between infection and premature labor is bacterial vaginosis (17, 18). There is also a considerable association between uterine infection and the commencement of spontaneous labor. Unplanned preterm birth is connected with increased risk for histopathological chorioamnionitis. Histologically proven chorioamnionitis is seen in about 90% of cases before delivery, and only 10% had evident clinical signs of infection (19, 20). Urinary tract infection is the commonest cause of an

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extrauterine infection, which occurs in approximately 5–10% of preterm labor (19). Romero and Mazor's results suggest that preterm labor may be due to an extrauterine infection by a mechanism in which the amnion produces PG in response to the creation of IL and TNF by maternal macrophages (19).

4. Hemorrhage:-

Placental abruption occurring prior to the birth of the infant may result in premature labor. It is thought that this phenomenon happens as prostaglandin production is not involved but rather the secretion of thrombin, which induces myometrial contraction by the release of protease-activated receptors. Thrombin release from decidual hemorrhage may also lead to preterm labor in chorioamnionitis (3).

5. Uterine over distension:-

There are two main reasons why preterm labor is more likely with multiple pregnancies. The first is the uterus getting too big, which causes too much regulation of proteins and hormones that are involved in contractions and cervical ripening. Mechanical strain affects all these variables and proteins. Numerous pregnancies are associated with an earlier increase in placental CRH concentration in the circulation because of the presence of multiple placentas (2, 3).

Risk group:-[1,2,3,9]

1. Following one preterm delivery, the risk of having a second preterm delivery is approximately 20%. After two preterm deliveries, the risk of a third preterm delivery is 35-40%.
2. Overdistension of the uterus: Particular care should be taken in multiple pregnancies or in cases suspected of polyhydramnios.
3. Procedures of the cervix for uterine malformations (e.g., cone biopsy).
4. Include current pregnancy factors:-

The simultaneous presence of more than one medical disease.

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Surgeon.

• Bleeding that stops for a while then starts again

A few low-level hazard factors include 1, 2, and 3.

1. Use of tobacco products.
2. Extremely low body mass index (BMI)
3. Pregnancy intervals less than 1 year.
4. Age of mother (adolescent, postpartum)
5. Race (Black women)
6. Socio-economic disadvantages.
7. Very little education.
8. Pregnancy termination.

Diagnosis of preterm labour

History:

Real and false labor are difficult to distinguish until there is visible dilatation and effacement of the cervical canal. The first sign that a woman is in labor when she has a high risk of postpartum bleeding is her obstetric history. Other signs that she may be about to go into labor include pelvic pressure, period-like cramping, watery vaginal discharge, and lower back pain.

• Previous obstetric history. In the event of one previous preterm birth, the risk of recurrent preterm delivery is four times greater than that of a term delivery. A history of term births followed by preterm deliveries has a higher risk of premature labor and delivery (PTL) than vice versa, as the last term of a term delivery could injure the cervix (5).

Examination:

Physical examination of the abdomen may reveal abdominal pain, suggestive of chorioamnionitis or abruption. A comprehensive speculum examination performed by a qualified doctor can find information such as the presence of abnormal discharge, pooling of amniotic fluid, or blood. You can usually tell if your dilation of the cervix is noticeable. Prostaglandin synthesis may be increased

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by digital examinations, and there is a potential for introducing infections into the cervical canal, so they should be utilized with caution (8).

Investigation:

1. Pregnant women at a high risk of PTL, including those with a history of problems during pregnancy or other medical disorders, should be screened for BV, as the virus is known to increase the risk of PTL (22).

2. Cervical length measurement by transvaginal ultrasound can aid prediction of risk of preterm labor in both high- and low-risk pregnancies. There are two primary ways currently: either measuring the cervical length frequently across the second and early third trimesters of pregnancy or measuring it once, sometimes at the usual ultrasound at 18-22 weeks. The presence or absence of funnelling is less predictive of preterm delivery than an absolute cervical length. (5)

3. Other investigations have included cervico-vaginal fetal fibronectin, salivary estriol, and corticotropin-releasing hormone (23, 24, 25, 26, 27). Fibronectin is a glycoprotein located in amniotic fluid, the placenta, and the decidua. Mechanical and inflammatory activities that precede labor promote its creation and release. Commonly found in vaginal discharge during the first 20 weeks, fibronectin levels typically decrease thereafter.

missed the first 36 weeks. One of the ways to predict postterm labor is to search for fibronectin in vaginal secretions between weeks 20 and 36. The probability of PTL within 7 days in a symptomatic woman with a positive FFT is approximately 40%. If the FFT is negative, the probability of delivery within 7 days is less than 1% (5).

Thrombin: The last step of the blood coagulation cascade is the activation of the serine protease thrombin from the zymogen prothrombin and conversion of fibrinogen to fibrin [29]. Thrombin acts in a similar manner in cellular activation as it does in the coagulation cascade. It affects cytokine production, modifies vascular and nonvascular muscle contraction, activates platelets, regulates blood

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vessel diameter, etc. [30–35]. In addition, fibrinogen-like protein 2 (FGL2), a tissue prothrombinase, can convert prothrombin to thrombin in tissues (without activating the coagulation cascade) [36].

Thrombin receptor: 1. The thrombin family of drugs activates a class of receptors called PARs that are involved in transmembrane G-protein coupling, allowing the drug to exert its effects on cells [37]. The four major subtypes of PARs are F2R, F2RL1, F2RL2, and F2RL3, alternatively called PARs 1, 2, 3, and 4. F2RL1 is activated by trypsin, whereas F2RL2, F2RL3, and F2RL3 are activated by thrombin. Various cell types and tissues such as endothelial cells, fibroblasts, platelets, smooth muscle (vascular and nonvascular), and others express the PARs [37].

Thrombin production:

During the luteal phase of the menstrual cycle, decidualization is driven by progesterone (P4), and estradiol (E2)-primed human endometrial stromal cells express the transmembrane 45-kDa glycoprotein, tissue factor (TF). Tissue factor (39, 40), abundant in decidual cells, is one of the primary factors that begin hemostasis. Decidual cell (DC) tissue factor is primed to activate factor X after abruption-related hemorrhage by binding to plasma-derived factor VIIa. The reaction proceeds by factor Xa complexing with factor Va to convert prothrombin to thrombin. The latter stimulates platelets and converts fibrinogen to fibrin. This process is in line with determining the severity of abruption, which is commonly assessed by the consumption of fibrinogen.

Furthermore, elevated blood levels of the thrombin-antithrombin complex can predict preterm delivery due to preterm labor and PPROM with high accuracy and specificity. (41–43)

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Mechanism of action:

Decidual thrombin generation is important in PPROM and PTL with abruption [44]. In vitro studies have revealed that thrombin acts on cultivated term DCs via the protease-activated receptor (PAR-1) and induces the synthesis of matrix metalloproteinases 1 and 3 (MMP-1 and -3). The MMPs, which break down the cellular matrix (45, 46), are significantly increased in PPROM and cervical changes before labor. Thrombin greatly increases the amount of IL-8 mRNA and protein in long-term DC cultures (45–47). Neutrophil infiltration is a rich source of proteases that degrade the extracellular matrix and may enhance the intense degradation of the extracellular matrix that characterizes fetal membrane rupture (50-52). Interleukin-8 (IL-8) is a potent chemoattractant and stimulator of neutrophils (49). We used picro-Mallory staining and showed that the increased neutrophil count associated with abruption colocalized with increased decidual fibrin deposition. (48) The amniochorion selectively degrades proteins of the basement membrane type, and thrombin increases the synthesis of matrix metalloproteinase-9 (53). Moreover, thrombin directly affects human fetal membranes, causing changes compatible with abruption-related PPROM. Thrombin causes tissue remodeling and apoptotic indicators that directly degrade preparations of amniotic membrane (54). The amniotic membrane is the principal load-bearing structure of the fetal membrane.

Thrombin and progesterone:

In mammals, high P4 levels maintain the myometrium in a quiescent state throughout pregnancy. (55) In most mammals, labor begins with a decrease of P4 levels in the blood. However, in humans and some higher primates, both placental and plasma P4 production and levels remain elevated until birth. The results of this investigation indicate that P4 withdrawal-induced parturition is mediated by a reduction in uterine progesterone receptor (PR) levels and/or a transition to defective PR isoform dominance. (56) Thrombin has been proposed to induce

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functional P4 withdrawal in abruption-associated PTD, and this may be one mechanism that initiates or contributes to the proparturition effects. This is supported by the obvious participation of excess DC-derived thrombin production during abruption and the demonstration that decreased PR expression in DCs is associated with term parturition (57). (44)

Role of the thrombin in preterm labour:

Normal pregnancy has been connected with an overproduction of maternal thrombin [58, 42] and a propensity to consolidate platelets in response to agonists [59, 60]. Other obstetric disorders with increased thrombin generation in maternal circulation are preterm labor (PTL) [42, 43], preeclampsia (61), fetal development limitation [61, 62], and premature prelabor rupture of membranes (PROM) [42, 41].

Thrombin is a powerful uterotonic agonist and is a component of the coagulation cascade. In those in vitro investigations, thrombin was found to potentiate myometrial contractions to a large extent, even at modest dosages of 1 U/mL. (63) Thrombin has a pronounced effect on the contractility of the uterus, and this is of physiological importance. 1 ml of clotted blood yields 130 to 160 units of thrombin. Further in vivo work on pregnant and nonpregnant rats showed that intraluminal injection of actively clotting blood was able to significantly enhance uterine contractions, whereas equal volumes of heparinized blood did not significantly influence myometrial contractions. Those investigations [64] have shown that the increased myometrial activity observed with illnesses linked with clinically evident intrauterine bleeding, such as placental abruption, has a molecular foundation. Some cases of “idiopathic” premature labor may have a mechanistic explanation, including subclinical decidual hemorrhage, since even low levels of thrombin can dramatically accelerate uterine contractions. 64, 63

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Thrombin-anti thrombin complex:

In cases of moderate or occult intrauterine hemorrhage, it may be difficult to clinically identify a relationship between thrombin activation and premature labor. Therefore, biological markers of thrombin activity would have to be used. As it is difficult to measure thrombin directly nowadays, thrombin generation activation and the coagulation cascade have been evaluated by indirect measurements. The usefulness of these indirect tests for thrombin has been confirmed by several studies in the hematologic literature. The concentration of active thrombin bound to antithrombin III, an endogenous thrombin antagonist, can be determined by a blood test known as thrombin-antithrombin III (TAT) complex levels (65, 66). The thrombin-antithrombin (TAT) III complex is a stable, inactive intermediate of the reaction of thrombin with its major inhibitor, antithrombin III. The detection of peptides released by zymogens or complexes formed between activated coagulation factors and their natural inhibitors is an indispensable tool for the investigation of the activation of the coagulation system. This is owing to the fact that active coagulation factors are difficult to detect directly during activation of the coagulation cascade and have a short half-life [67]. The presence and/or the concentration of TAT III complexes is generally considered an indicator of thrombin production in vivo [65-66-68-69]. Higher thrombin-antithrombin (TAT) concentrations have been observed in patients with active preterm labor compared with normal controls by Elovitz et al. [43] and Chaiworapongsa et al. [42]. Those who failed tocolysis and later delivered had much larger quantities. Subclinical choriondecidual hemorrhage would probably have occurred in these patients even without placental pathologic findings. Other studies have linked increased TAT levels in asymptomatic individuals with PPROM [41] and SPTB [70]. [70] The end result was the High plasma concentrations of TAT III complexes are not associated with a history of vaginal bleeding during pregnancy [42, 43] or with the presence of intra-amniotic infection/inflammation (IAI) [42]. This finding shows that independent of the

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mechanism(s) precipitating preterm parturition syndrome (71-77), an episode of PTL is associated with activation of the maternal coagulation cascade. The higher level of TAT in the uterine vein than in the systemic circulation (78) may reflect increased thrombin activation in the uterus.

Patients & Methods

This case control study included 85 pregnant women presented to Tikrit teaching hospital from January 2013 to January 2014.

The ethics approval was obtained from the Scientific Council for Obstetrics and Gynaecology Specialisation and Hospital Administration in Iraq. All patients were requested to provide consent verbally.

• The initial study population was 55 women. All women were pregnant , 60 of them were hospitalised to the obstetrics and gynaecology department of the hospital with the diagnosis of imminent preterm labour (24-34+6) weeks of their pregnancies.

• Twenty-five women with no history of preterm labour or delivery were recruited from the outpatient clinic and were all included in the control group which comprised women with gestational ages ranging from twenty-four to thirty-four and a half weeks. All of these women had normal pregnancies with a single baby We welcomed women who were expecting a child and whose ages were between 18 and 45.

Demographic data of the patients were taken into account and their gestational age was estimated using the menstrual date which was accurately remembered (as they were regular menstruators) and ultrasound scans performed in the first or early second trimester to verify accuracy.

Inclusion criteria for study group were:

A single mother's pregnancy.

•cell walls perfectly intact.

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1. no cerclage.

with a cervical dilation of less than 3 centimetres.

Exclusion criteria included:

Vaginal bleeding

• Neonatal clinical presentation mimicking abruption

• suspected or identified chorioamnionitis.

• a minimum of two pregnancies.

Preeclampsia, a medical disorder.

• Known or suspected thromboembolic disease;

• Recent or chronic congestive heart failure diagnosis or history.

• Medical problems that preclude tocolysis.

• Evidence of incomplete foetal development.

• Sonographic evidence of congenital anomalies.

A detailed medical history was taken from each patient in our study group including their age, occupation, gynaecological history and obstetrical history and any previous medical conditions. The mother's heart rate, blood pressure, temperature and pace of breathing were observed. Obstetrician assessed foetal heart rate (FHR) and uterine contraction using abdominal and pelvic examination. On admission, the research group had diagnostic investigations including a haemogram, urine microscopy and abdominal US. All patients received the oral tocolytic nifedipine 10 mg every 8 hours. They each received a single course of treatment, consisting of a 12-milligram injection of betamethasone within one day of admission.

Venous blood (4-5 mL) was collected in a tube containing sodium citrate anticoagulant, in both study and control groups. The tube was inverted several times and taken directly to the coagulation laboratory at Tikrit Teaching Hospital for processing. The blood was then spun in a centrifuge to separate the plasma from the platelets then spun again to make plasma. The plasma was then transferred to plastic tubes and frozen at -20°C.

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The TAT levels in each sample were determined by an enzyme-linked immunoassay. TAT can be detected from 62.5 pg/ml to 4000 pg/ml. The lowest TAT concentration detectable in humans is less than 15.6 pg/ml in most of cases. The lowest protein concentration that can be separated from zero is called the Lower Limit of Detection (LLD) and is used to describe the sensitivity of this test. This assay is very sensitive and has exceptional specificity for the detection of human TAT. Recording of vitals (pulse rate, blood pressure, uterine contractions and foetal heart rate) was done to all the patients. The exact time of delivery was determined by following up on the two groups. Follow up appointments are a common part of our outpatient clinic when we see our patients to see how their pregnancy is doing and when they might expect to give birth. Each patient was counselled about any new symptoms such as nausea, vomiting, fever, vaginal discharge or bleeding or a decrease in foetal activity before discharge home.

Steps of TAT Management

1. Prepare all the materials including the reagents, the samples and the standards.
2. Add 100 µl of the standard or sample to each well. Incubate for 2 h at 37°C.
3. Remove contents of each well without washing.

Add 100µl of biotin-antibody (1x) to each well. Incubate 1 h at 37 °C.

5. Aspirating, rinse three times.
6. Add 100µl HRP-avidin (1x) to each well. Incubate at 37°C for 1 hour.
7. Rinse 5 times and aspirate.
8. Add 90 µl of TMB substrate to each well. Incubate at 37°C for 15-30 minutes. Stay out of the light.

50 µl stop solution was added to each well. Incubate for 5 min and read at 450 nm.

Statistical Analysis and Data Management

Data were entered and analysed by Statistical Package for Social Sciences version 18. The chi-square test of association was used to examine proportions of

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different features among cases and controls with the same proportions. Cases and controls were compared using Unpaired Student t tests, one- and two-way analysis of variance and Pearson correlation was used to measure the degree of inter- and intra-group correlation. A p-value of less than or equal to 0.05 was determined to be statistically significant. The ROC curve is used to establish the sensitivity and specificity levels, and the cutoff thresholds.

Results

Table 1: The study group distribution according to age

Age	Study groups		Total
	Control	Preterm	
< 20 years	3 (12.0%)	12 (20.0%)	15 (17.6%)
20-30 years	18 (72.0%)	36 (60.0%)	54 (63.5%)
>30 years	4 (16.0%)	12 (20.0%)	16 (18.8%)
Total	25 (100.0%)	60 (100.0%)	85 (100.0%)

$X^2 = 1.190$, df = 2, p-value = 0.552 (> 0.05 not significant)

Table 2 shows the relation between parity and age group which reveal that 22 (36.7%) of women who have PTL was primigravida of them ten (10) their age group was <20 years old.

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Table 2: The relation between parity and age group among cases and control groups

Group	Parity	Age Group			Total	P value
		< 20 years	20-30 years	>30 years		
Control	Primi-gravida	3 (100%)	3 (16.7%)	0 (0%)	6 (24%)	X^2=11.294 df=2 pvalue=0.004 (<0.05 sig)
	Multi-gravida	0 (0%)	15 (83.3%)	4 (100%)	19 (76%)	
	Total	3 (100%)	18 (100%)	4 (100%)	25 (100%)	
Preterm	Primi-gravida	10 (83.3%)	12 (33.3%)	0 (0%)	22 (36.7%)	X^2=18.373 df=2 pvalue=0.0001 (<0.05 sig)
	Multi-gravida	2 (16.7%)	24 (66.7%)	12 (100%)	38 (63.3%)	
	Total	12 (100%)	36 (100%)	12 (100%)	60 (100%)	

Table 3 shows distribution of study groups according to blood group which reveal that 44 (51.80%) women of both studied group was O+.

Table 3: The distribution of study groups according to blood group

Blood group	Study groups		Total
	Control	Preterm	
A+	3 (12.0%)	10 (16.7%)	13 (15.3%)
B+	7 (28.0%)	10 (16.7%)	17 (20.0%)
AB+	1 (4.0%)	2 (3.3%)	3 (3.5%)
O+	9 (36.0%)	35 (58.3%)	44 (51.8%)
B-	1 (4.0%)	2 (3.3%)	3 (3.5%)
AB-	4 (16.0%)	1 (1.7%)	5 (5.9%)
Total	25 (100%)	60 (100%)	85 (100%)

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$X^2 = 9.293$, df = 5, pvalue = 0.098 (> 0.05 not significant)

Figure 1 shows that About 12 preterm cases (20%) had history of preterm labor, in comparison to 48 (80%) had no history.

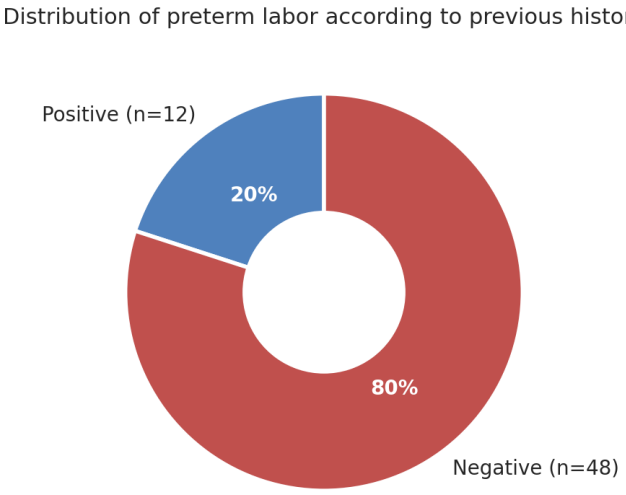

Figure 1: The distribution of preterm labor according to previous history of preterm labor

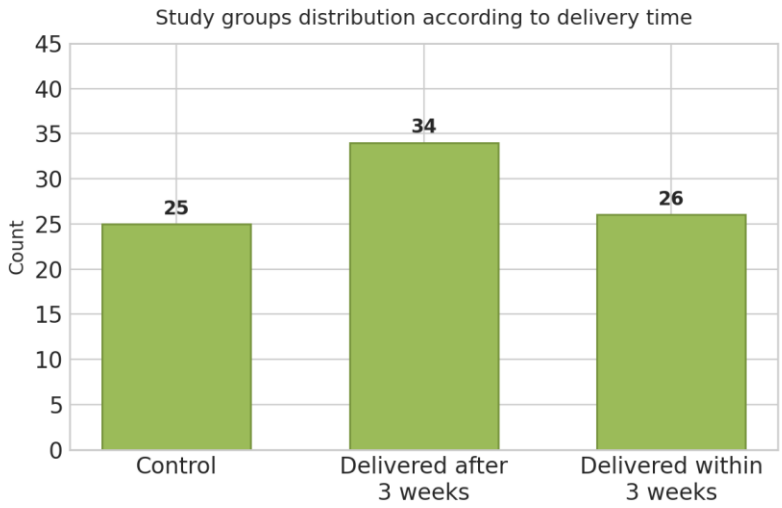

Figure 2: The study groups distribution according to delivery time

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Table 4 shows the Mean TAT level among study groups which reveal that 26 patients from those who have PTL have mean TAT level 154.23 delivered within 3 weeks of admission. This level is higher than those patients with PTL who delivered after 3 weeks of admission their mean TAT level was 92.94 or control patient who delivered at term with TAT level 83.00.

Table 4: The Mean TAT level among study group and control.

Group	N	Mean	Std. Deviation	Minimum	Maximum	Median
Control	25	83.00	18.45	62.00	122.00	72.00
Delivered after 3 weeks	34	92.94	15.30	62.00	118.00	93.00
Delivered within 3 weeks	26	154.23	27.81	124.00	202.00	135.50
Total	85	108.76	36.86	62.00	202.00	103.00

F = 91.737, df = 2, P value = 0.0001 (< 0.05 significant) (one way ANOVA)

Figure 3 shows that TAT level is higher in patient who delivered within 3 weeks.

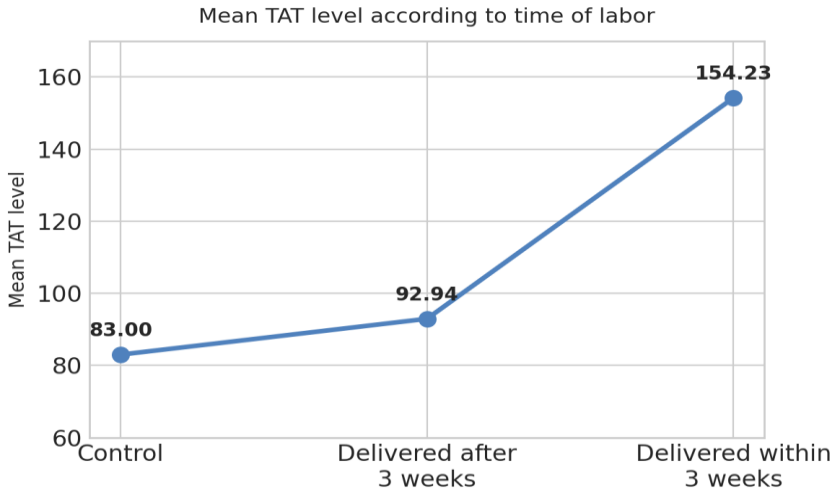

Figure 3: The mean TAT level according to time of labor

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Table 5 shows the distribution of study groups according to mode of delivery which reveal that 74 women (87.1%) of both study groups delivered by NVD and 11 (12.9%) women delivered by C/S.

Table 5: The distribution of study groups according to mode of delivery

Mode of delivery	Study groups		Total
	Control	Preterm	
Normal vaginal delivery	22 (88.0%)	52 (86.7%)	74 (87.1%)
Caesarean section	3 (12.0%)	8 (13.3%)	11 (12.9%)
Total	25 (100%)	60 (100%)	85 (100%)

$X^2 = 0.028$, df = 1, pvalue = 0.528 (> 0.05 not significant)

Table 6 shows the mean TAT level for patients who delivered vaginally was (107.97±36.6) which does not differ significantly from TAT level for those who delivered by C/S their TAT level was 114.1±39.64.

Table 6: The mean TAT level according to mode of delivery and time of labor.

Mode of delivery	Control (n=25)	Delivered after 3 weeks (n=34)	Delivered within 3 weeks (n=26)	Total	ANOVA p-value
Normal Vaginal Delivery	n=22 84.63±19.31	n=32 93.65±15.5	n=20 156.85±29.14	107.97±36.6	F = 63.165, df = 2, p = 0.0001 (<0.05 sig)
Caesarean Section	n=3 73±1	n=2 81.5±0.7	n=6 145.5±2.8	114.1±39.64	F = 14.545, df = 2, p = 0.002 (<0.05 sig)
Independent t-test	T = 2.72, df = 23, p = 0.013 (<0.05 sig)	T = 1.233, df = 32, p = 0.226 (>0.05 non-sig)	T = 0.973, df = 24, p = 0.34 (>0.05 non-sig)	T = 0.287, df = 83, p = 0.775 (>0.05 non-sig)	

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Table 7: The Mean TAT level among different study groups according to blood group

Blood Group	Control		Delivered after 3 weeks		Delivered within 3 weeks		Total	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A+	73.00	1.00	105.25	13.31	129.50	0.71	101.54	21.13
B+	74.00	21.39	85.17	16.80	188.00	15.60	104.76	50.95
AB+	107.00	-	-	-	186.50	0.71	160.00	45.90
O+	80.56	16.18	91.17	13.08	147.00	23.86	110.57	34.63
B-	109.00	-	83.00	18.38	-	-	91.67	19.86
AB-	99.25	5.85	-	-	127.00	-	104.80	13.41
Total	83.00	18.45	92.94	15.30	154.23	27.81	108.76	36.86

Two way ANOVA test indicate significant variation for time of delivery on TAT level ($F=42.989$, $P = 0.00001 < 0.05$), significant variation for blood group ($F=2.495$, P value$= 0.039 < 0.05$), and significant variation for interaction between blood group and time of labor ($F=4.537$, P value$=0.0001 < 0.05$).

Table 8: The Mean TAT among different level study groups according to age

Age	Control			Delivered after 3 weeks			Delivered within 3 weeks		
	N	Mean	Std. Dev	N	Mean	Std. Dev	N	Mean	Std. Dev
< 20 years	3	73.00	1.00	10	95.80	11.46	2	174.50	0.71
20-30 years	18	85.83	17.16	16	97.63	13.30	20	152.65	29.35
> 30 years	4	77.75	29.51	8	80.00	17.40	4	152.00	26.37
Total	25	83.00	18.45	34	92.94	15.30	26	154.23	27.81

Two way ANOVA test indicate significant variation for time of delivery ($F= 47.183$, $P=0.0001 < 0.05$), non-significant variation for age ($F= 1.214$,

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Pvalue=0.303 > 0.05), and non-significant variation for interaction between age and time of labor (F=0.948, P=0.441 > 0.05).

Pearson correlation show that, there is significant moderate negative linear correlation between TAT level and gestational age r = -0.622, as shown in figure 4, and with days spend to delivery r = -0.545, as shown in figure 5, which mean with low TAT the latency period between admission and delivery will increase.

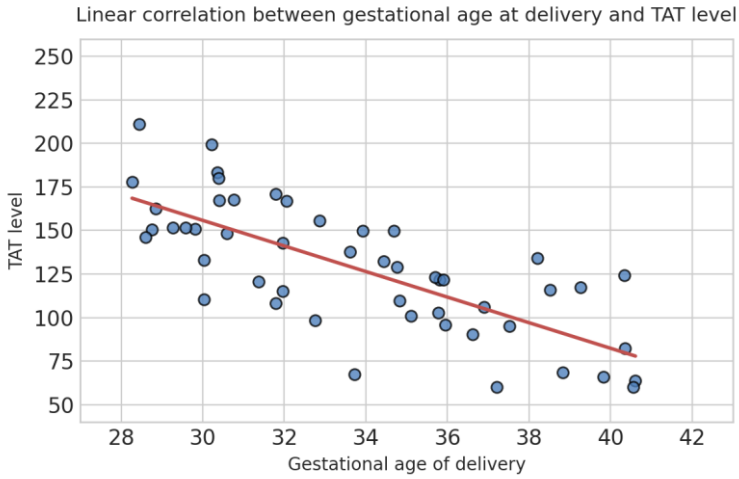

Figure 4: The linear correlation between gestational age at delivery and TAT level

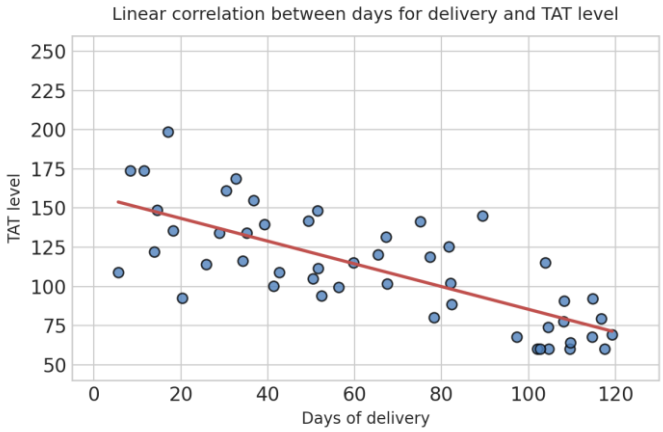

Figure 5: The linear correlation between days for delivery and TAT level

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Receiver Operating Characteristic (ROC) Curve Analysis

ROC analysis was used to evaluate the diagnostic value of TAT level in predicting preterm delivery. For predicting preterm delivery within 3 weeks, a cut-off point of > 120 pg/ml was identified.

Table 9: The sensitivity, specificity for the cut-off point > 120 to detect delivery within 3 weeks

Parameter	Value
Cut-off point	> 120 pg/ml
Sensitivity	92.3%
Specificity	100.0%
Positive Predictive Value (PPV)	100.0%
Negative Predictive Value (NPV)	96.7%

For predicting preterm delivery within 7 days, a higher cut-off point of > 132 pg/ml was identified, providing improved prognostic parameters for imminent preterm labor.

Table 10: The sensitivity, specificity for the cut-off point > 132 to detect delivery within 7 days

Parameter	Value
Cut-off point	> 132 pg/ml
Sensitivity	100.0%
Specificity	96.6%
Positive Predictive Value (PPV)	81.8%
Negative Predictive Value (NPV)	100.0%

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Discussion

Preterm labour (PTL) remains one of the leading causes of perinatal morbidity and mortality worldwide and represents a major public health challenge. In addition to its medical consequences, PTL has profound social and psychological impacts on affected families, often compromising the expectation of delivering a healthy infant. Therefore, identifying reliable predictors of preterm labour is of considerable clinical importance. In recent years, several novel biomarkers have been investigated as potential predictors of spontaneous preterm birth, particularly in low-risk pregnancies, with the aim of improving early diagnosis and optimizing clinical management (79,80). The diagnosis of true preterm labour continues to present a significant challenge for obstetricians. Owing to the serious neonatal complications associated with preterm birth, many women presenting with symptoms of PTL receive tocolytic therapy and corticosteroids despite the uncertainty regarding the likelihood of imminent delivery. However, evidence suggesting limited benefit from repeated corticosteroid administration, together with the potential adverse effects of tocolytic agents, highlights the need for more accurate biomarkers capable of identifying women at genuine risk of preterm delivery (81,82). Several investigators have evaluated thrombin generation, assessed by measuring thrombin–antithrombin (TAT) complexes in maternal plasma, as a potential predictor of PTL. The findings of the present study demonstrated that maternal plasma TAT levels were significantly higher among women with preterm labour who subsequently delivered before term compared with those who delivered at term. A significant association was observed between maternal plasma TAT concentration and the timing of delivery. Women who delivered within three weeks of admission had significantly higher mean TAT levels than both the control group and women with PTL who delivered more than three weeks after admission. In contrast, no statistically significant difference in TAT levels was found between the control group and women with PTL who ultimately delivered at term. Furthermore, women who eventually delivered

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preterm exhibited higher maternal plasma TAT concentrations than controls. Our findings also suggest that increasing TAT levels are associated with a shorter latency interval between the onset of preterm labour and delivery. A TAT cut-off value greater than 120 ng/mL predicted delivery within three weeks with a sensitivity of 100%, specificity of 98%, and overall diagnostic accuracy of 99%. Similarly, a cut-off value greater than 132 ng/mL predicted delivery within seven days with a sensitivity of 100%, specificity of 87%, and diagnostic accuracy of 88%. The present study also demonstrated that maternal plasma TAT levels were not associated with the mode of delivery, as no statistically significant differences were observed between women who delivered vaginally and those who underwent cesarean section.

An interesting finding was the significant association between maternal plasma TAT levels, ABO blood group, and the timing of delivery. The highest mean TAT concentration was observed among women with blood group B-positive (188.00 ng/mL), followed by those with AB-positive blood group (186.50 ng/mL), particularly among patients who delivered within three weeks of admission. The findings of this study are consistent with those reported by Elovitz et al. (2001), who demonstrated significantly elevated plasma TAT concentrations in women with preterm labour who subsequently delivered preterm, supporting the role of thrombin activation in the pathophysiology of PTL. Similarly, Rosen et al. (2001) reported that elevated maternal plasma TAT concentrations during the second trimester were predictive of subsequent preterm premature rupture of membranes (PPROM), providing further evidence that decidual thrombin activation contributes to adverse pregnancy outcomes (41). The results are also supported by Chaiworapongsa et al. (2002), who conducted a cross-sectional study demonstrating excessive thrombin generation in women with preterm labour and preterm premature rupture of membranes, further confirming the involvement of coagulation activation in PTL (42).

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In another study, Rosen et al. (2002) proposed that thrombin-induced expression of matrix metalloproteinase-1 (MMP-1) in decidual and endometrial stromal cells may explain the strong association between placental abruption and premature rupture of fetal membranes, thereby supporting the biological mechanism linking thrombin activation with preterm birth (86). Likewise, Erez et al. (2009) reported that thrombin possesses potent uterotonic properties and that increased activation of thrombin is associated with spontaneous PTL. Their study demonstrated that women with elevated amniotic fluid TAT III complex concentrations had a significantly greater risk of preterm delivery, suggesting that increased thrombin activity may represent an important component of intra-amniotic inflammation (84) Further evidence was provided by Erez et al. (2010), who observed increased thrombin generation in both maternal plasma and amniotic fluid among women with PTL. They suggested that activation of the extrinsic coagulation pathway, together with reduced anticoagulant activity reflected by lower maternal tissue factor pathway inhibitor (TFPI) concentrations, may contribute to excessive thrombin generation during preterm labour (83).

Our findings are also in agreement with Lockwood et al. (2012), who demonstrated that thrombin generated during active coagulation exerts powerful uterotonic effects independent of prostaglandin synthesis. These observations provide a plausible explanation for the increased uterine contractions observed in cases of intrauterine bleeding and support the hypothesis that thrombin generation contributes to the initiation of preterm labour through decidual progesterone withdrawal and activation of parturition pathways (44,64,85). In contrast, David N. et al. (2010) reported findings that differed from the present study. They observed significantly lower maternal plasma TAT concentrations in asymptomatic women who subsequently delivered before 37 weeks of gestation compared with matched controls. The authors proposed that elevated TAT levels observed in women presenting with acute PTL may reflect subclinical chorio-decidual hemorrhage and acute thrombin activation, whereas asymptomatic

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women may exhibit only baseline thrombin production. Consequently, the two populations may not be directly comparable (87). To the best of our knowledge, this study represents the first investigation conducted in Iraq evaluating maternal plasma thrombin–antithrombin complexes as a biomarker for predicting spontaneous preterm labour. The findings suggest that maternal plasma TAT concentration is a promising predictor of preterm delivery and may have potential clinical value in identifying women at high risk for imminent preterm birth.

Conclusion:

TAT test is highly sensitive and specific and the TAT level were significantly higher in symptomatic women with threatened preterm birth who gave preterm labour especially those who deliver within 3 weeks.

Recommendations further studies in future.

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