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The Role of Acute Phase Reactants (Fibrinogen, Ferritin, Albumin, Calcium) in Pregnant Women with Preterm Delivery

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Abstract:

Background: Preterm labor and related prematurity are predisposing factors that increase perinatal morbidity and mortality. Acute phase reactants are inflammatory markers which are positive and negative reactants explained by the reaction of reactants to the subclinical infection that are commonly associated with preterm labor.

Objectives: To assess the role of acute phase reactants in pregnant women with preterm delivery.

Patients and method: A case control study conducted in Gynecological Department of Baghdad Teaching Hospital from 1st February 2021 to 30th October 2021, on one hundred pregnant women with gestational age (28weeks - 36weeks+6days) who attended outpatient clinic; fifty pregnant women with established preterm labor as case group and fifty pregnant women with no signs and symptoms of preterm labor as control group. Data was collected using structured questionnaire included demographic features, and biochemical parameters (serum ferritin (ng/ml), albumin (gm/dl), fibrinogen (mg/dl), and calcium (mg/dl) .

Results: Mean±SD serum ferritin in control group was (46.2 ± 16.2 ng/ml) while in case group (52.47 ± 11.6ng/ml) with significant difference between both groups (P=0.03), mean±SD serum albumin in control group (3.18 ± 0.31 ng/ml) while in case group (2.92 ± 0.39) with highly significant difference between both groups (P<0.001). Validity test of serum ferritin at cutoff ≥ 52.7 (ng/ml) in case group was as follows: Sensitivity (94%), specificity (90%), negative predictive value (94%), positive predictive value (90%) and the accuracy was (92%). The validity test of serum albumin at cutoff ≤ 3.06 (gm/dl) to detect the preterm labor as follows: Sensitivity (78%), specificity (86%), negative predictive value (78%), positive predictive value (83%) and the accuracy was (84%). Mean±SD serum fibrinogen in control group was (400.9 ± 38.1) while in case group was (410.7 ± 51.2) with no significant difference between both groups (P=0.1). Mean±SD serum calcium in control group was (8.1 ± 0.7) while in case group was (7.92 ± 0.5) with no significant difference between both groups (P=0.1).

Conclusion: serum ferritin and albumin can be used in prediction of preterm labor in 3rd trimester.

Keywords: Acute Phase Reactants, Albumin, Ferritin, Fibrinogen, Preterm Delivery.

Introduction:

Preterm birth is defined as delivery of a baby before 37 completed weeks of pregnancy. Legally, in the UK, the 1992 Amendment to the Infant Life Preservation Act defined the limit of viability as 24 weeks. However, a small number of infants born at 23 weeks will survive (1). Preterm labor is divided into**:** late preterm labor (34 weeks to 36 wks. and 6 days); moderate preterm labor (32 wks. to 33 weeks and 6 days); very preterm labor (28 wks. to 31 weeks and 6 days); and extreme preterm labor (<28 weeks). (2) The majority of Preterm labor are late, the prevalence of late labor elevated from (7.28%; 2018) to (7.46%; 2019). Moderate preterm labor elevated from (2.75%; 2018) to (2.77%; 2019). (2) Globally; 11.5% of all newborns are preterm each year (3). Etiology of preterm labor may be vascular disease, and breakdown in maternal–fetal tolerance, uterine over distension, maternal stress, cervical weakness (4-9); or infection. (10-12) Low socioeconomic status, poor antenatal care, extremes of maternal age and malnutrition, low maternal pre-pregnancy body mass index (19.8 kg / m2 or less), maternal smoking, substance abuse, alcohol consumption, heavy physical work, and a short pregnancy interval (less than 18 months between pregnancies), cervical issues, uterine

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malformation, prior history of preterm birth; are considered risk factors for preterm delivery (13-15).

Acute phase reactants (APR) are inflammatory markers which show significant changes in serum concentration during inflammation. Two types of serum APR; high which are considered positive and low which considered negative in the serum by at least 25% and show changes in hepatocytes production(16). APR are potential for liver [Changes in the levels of APR largely reflect altered production by hepatocytes, resulting primarily from the effects of cytokines produced during the inflammatory process by macrophages, monocytes, and a variety of other cells. However, the highest levels are attained in acute inflammation during an acute infection or after trauma. Interleukin-6 (IL-6) produced by kupffer cells in the liver is the primary cytokine responsible for inducing the production of most APR]. During inflammatory state (acute and/or chronic). Changes in the levels of APR largely reflect altered production by hepatocytes, resulting primarily from the effects of cytokines produced during the inflammatory process by macrophages, monocytes, and a variety of other cells. However, the highest levels are attained in acute inflammation during an acute infection or after trauma. (16, 17). Positive APR are upregulated, while negative APR are downregulated, may be due to subclinical infection. Preterm may be associated with infection; thus, these moderators may be of benefit to predict preterm deliveries (16, 18).

Materials and Methods:

A case control study conducted at Obstetrics and Gynecology Department of Baghdad Teaching Hospital from the 1st February 2021 to 30th October 2021 after approval by the scientific council of the Iraqi Board for Medical Specialization in Obstetrics and gynecology. It is carried on one hundred pregnant women who attended outpatient clinic with gestational age from 28 weeks to 36 weeks and 6 days; and a verbal consent was obtained from them. They were divided into two groups:

1.Fifty pregnant women with singleton preterm pregnancy with no signs and symptoms of preterm labor attended for periodic check-up as control group.

2.Fifty pregnant women with singleton preterm pregnancy with established labor (three or more regular uterine contractions every 10 minutes, last more than 40 seconds, moderate to severe intensity, cervical dilatation ≥ 4 cm, 80% effacement) as cases group. They admitted to the labor ward of the department.

Data was collected from patients by using a specially designed questionnaire included: Demographic and Clinical features; with laboratory data for serum ferritin, serum albumin, serum fibrinogen, and serum calcium. The analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0. The *t*-test and chi square tests were used. ROC was done to identify the cutoff value to detect sensitivity and specificity of the test. Values were expressed as means± SD. P value of ≤ 0.05 regarded statistically significant.

Results

The main age of participants was 20-29 years (48%), then (35%) between 30-39 years, and (17%) aged <20 years. Participants with gestational age (28-32) weeks those with gestational age (33-36) weeks represented (44%). More than two-thirds (68%) of the studied groups were multigravida and less than one-third (32%) were primigravida. Less than two thirds (63%) of the women with (1-3) Parity, while (37%) of them with parity > 3 (Figure 1).

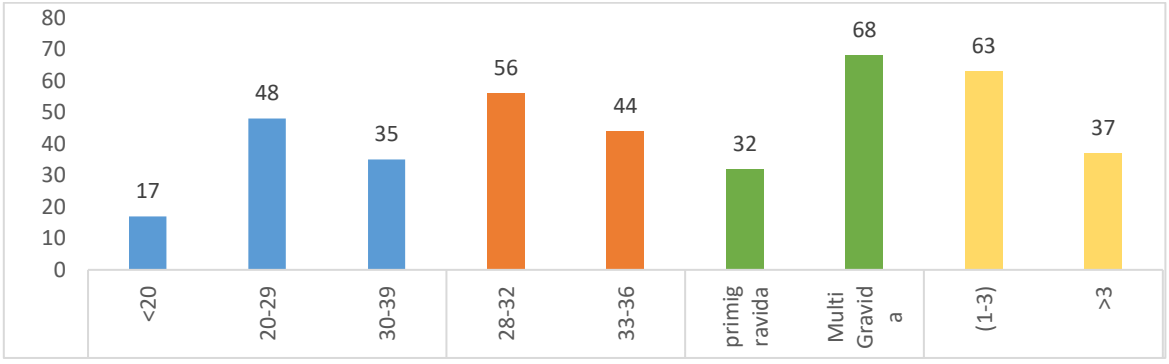

Figure 1: Demographic criteria of the studied groups.

Table (1) showsd he differences between Obstetrics and Acute phase reactants criteria in the studied groups. Mean± SD maternal age in control group was (26.3 ± 4.9) years while in case group was (26.7 ± 5.3) years with no statistically significant difference between both groups (P=0.6), Mean± SD gravidity in control group was (1.8 ± 0.7) while in case group was (1.9 ± 1.01) with no statistically significant difference between both groups (P=0.5), Mean± SD parity in control group was (0.7 ± 0.2) and in case group was (0.8 ± 0.4) with no

statistically significant difference between both groups (P=0.1). Mean± SD gestational age at delivery in control group was (32.3 ± 1.4) weeks while in case group was (32.1 ± 1.1) weeks with no significant difference between both groups (P=0.4). Mean± SD serum ferritin in control group was (46.2 ± 16.2) (ng/ml) while in case group was (52.47 ± 11.6) (ng/ml) with significant difference between both groups (P=0.03). Mean± SD serum albumin in control group was (3.18 ± 0.31) (gm/dl) while in case group was (2.92 ± 0.39) (gm/dl) with highly significant difference between both groups (P<0.001). Mean± SD serum fibrinogen in control group was (400.9 ± 38.1) (mg/dl) while in case group was (410.7 ± 51.2) (mg/dl) with no significant difference between both groups (P=0.1). Mean± SD serum calcium in control group was (8.1 ± 0.7) (mg/dl) while in case group was (7.92 ± 0.5) (mg/dl) with no significant difference between both groups (P=0.1; Figure 2).

Table 1: Differences between Obstetrics and Acute phase reactants criteria in the studied groups

Variable (mean± SD)	Control group (n=50)	Case group (n=50)	P value*
Maternal age (years)	26.3± 4.9	26.7± 5.3	0.6
Gravidity	1.8± 0.7	1.9± 1.01	0.5
Parity	0.7± 0.2	0.8± 0.4	0.1
Gestational age (weeks)	32.3± 1.4	32.1± 1.1	0.4
S. Ferritin (ng/ml)	46.2± 16.2	52.47± 11.6	0.03
S. Albumin (gm/dl)	3.18±0.31	2.92± 0.39	<0.001
S. Fibrinogen (mg/dl)	400.9±38.1	410.7±51.2	0.1
S. calcium (mg/dl)	8.1± 0.7	7.92± 0.5	0.1

***Independent *t*–test.**

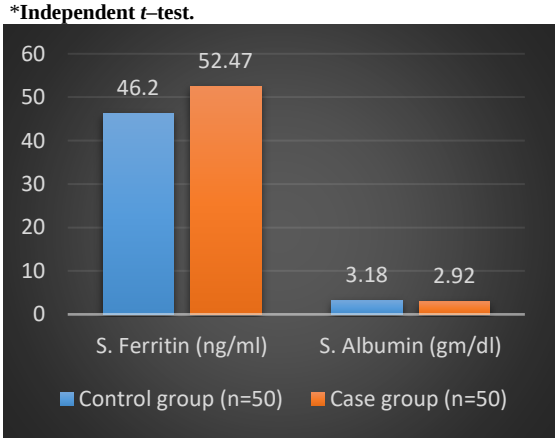

Figure 2: Distribution of mean serum levels of ferritin and albumin in the studied groups.

As shown in table (20, in mothers aged <20 years, the levels of serum ferritin in control and case groups were (51.2± 11.9 and 56.4±9.7ng/ml, respectively) with significant difference (P=0.01), while in mothers within the age group (20-29) years, were (48.3± 7.4 and. 54.1±11.2, ng/ml, respectively) with highly significant difference found (P<0.001), while for age group (30-39) years, levels of serum ferritin in control and case groups were (41.9±6.7 and 59.77±20.06 ng/ml, respectively; P<0.001). For primigravida, serum levels of ferritin in control and case groups were (44.5±13.3 and. 63.66± 14.7ng/ml, respectively; P<0.001), and in multigravida were (50.1±2.7 and 57.60±17.8ng/ml, respectively; P=0.004). In patients with (1-3); control group ferritin (44.3±13.9ng/ml) and for cases (54.0±21.1ng/ml) with significant difference between both groups (P=0.005), statistically significant in parity >3 (P<0.001). The levels of serum ferritin in gestational age (28-32) weeks was (44.63±7.2 and. 63.7±27.2ng/ml) in control and case group respectively) with highly significant difference (P<0.001). In gestational age (33-36) weeks were (46.79±10.4 and. 59.9±19.1ng/ml, respectively) with highly significant association.

Table 2: ferritin according to Patients' criteria in the studied group

Parameter		S. Ferritin (ng/ml)		P value *
		Control	Case	
Age Group (years)	<20	51.2± 11.9	56.4±9.7	0.01
	20-29	48.3± 7.4	54.1±11.2	<0.001
	30-39	41.9±6.7	59.77±20.06	<0.001
Gravida	Primigravida	44.5±13.3	63.66± 14.7	<0.001
	Multigravida	50.1±2.7	57.60±17.8	0.004
Parity	1-3	44.3±13.9	54.0±21.1	0.005
	>3	51.1±12.6	58.6±6.8	<0.001
Gestational age (weeks)	28-32	44.63±7.2	63.7±27.2	<0.001
	33-36	46.79±10.4	59.9±19.1	<0.001

***Independent *t*-test.**

As shown in table (3), in mothers aged <20 years, the serum levels of albumin in control and case groups were (3.29 ± 0.1 and. 3.15 ± 0.38gm/dl, respectively; P=0.01), while in mothers aged (20-29) years were (3.34±0.4 and 3.18±0.2gm/dl, respectively; P=0.003), for age (30-39) were (3.19±0.6 and 3.07±0.16gm/dl, respectively; P=0.04). For primigravida, the levels of serum albumin in control and case groups were (3.23±0.4 and 3.06± 0.7gm/dl, respectively; P=0.01), and in multigravida were (3.28±0.3 and 2.9± 0.02gm/dl, respectively; P<0.001). In patients with (1-3) parity the level of serum albumin in control group was (3.25±0.6gm/dl) and for cases was (3.06±0.1gm/dl) with significant difference between both groups (P=0.02), while in parity >3 the levels of serum albumin in control and case group were (3.15±0.8 and 3.08±0.1gm/dl, respectively; P=0.01). The levels of serum albumin in gestational age (28-32) weeks in control and case group were (3.2±0.2 and 2.8±0.2gm/dl, respectively; P<0.001), while in gestational age (33-36) the levels of serum albumin in control and case group

were (3.28±0.2 and 3.0±0.5gm/dl, respectively; P=0.02).

Table 3: Serum levels of albumin according to the Patients' criteria in the studied groups

Parameter		S. Albumin (gm/dl)		P value
		Control group	Case group	
Age Group (years)	<20	3.29±0.1	3.15±0.38	0.01
	20-29	3.34±0.4	3.18±0.2	0.003
	30-39	3.19±0.6	3.07±0.16	0.04
Gravida	Primigravida	3.23±0.4	3.06± 0.7	0.01
	Mulgravida	3.28±0.3	2.9± 0.02	<0.001
Parity	1-3	3.25±0.6	3.06±0.1	0.02
	>3	3.15±0.8	3.08±0.1	0.01
Gestational age (weeks)	28-32	3.2±0.2	2.8±0.2	<0.001
	33-36	3.28±0.2	3.0±0.5	0.02

***Independent *t*-test.**

Table 4 showed that the validity test of serum ferritin at cutoff ≥ 52.7 ng/ml in case group as follows: Sensitivity (94%), specificity (90%), NPV (94%), PPV (90%) and the accuracy was (92%). The validity test of serum albumin at cutoff ≤ 3.06gm/dl to detect the preterm labor as follows: Sensitivity (78%), specificity (86%), NPV (78%), PPV (83%) and the accuracy was (84%) (Figure 3).

Table 4: Validity test of serum ferritin and serum albumin to detect preterm labor in case group

Cutoff value	Sensitivity	Specificity	NPV	PPV	Accuracy
Serum ferritin at cutoff ≥ 52.7 (ng/ml)	94%	90%	94%	90%	92%
Serum albumin at cutoff ≤ 3.06 (gm/dl)	78%	86%	78%	83%	84%

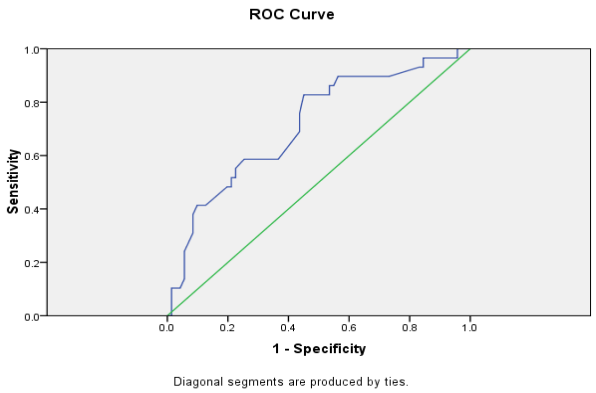

Figure 3: ROC curve for serum ferritin and serum albumin in case group (AUC=0.90).

Discussion:

Preterm labor and related prematurity are predisposing factors which increase perinatal morbidity and mortality. In addition, despite the recent development in perinatology &prenatal treatment, the mechanisms of induction of preterm uterine contractility remain unknown, therefore it is still important to find non-expensive methods which allow predicting preterm delivery. Moreover, when women present with symptoms of threatened preterm labor and if the likelihood of having spontaneous preterm birth can be identified, interventions can be taken to prevent or delay birth and to improve neonatal outcome (19). It has been demonstrated that placental isoferritin, a placental isoform ferritin, is present in the syncytiotrophoblast (20). The Elevated serum ferritin concentrations may indicate the exposure to an infectious agent or presence of any condition non-infectious inflammatory disease together with an adequate level of iron ions, a possible association between elevated serum ferritin concentrations and fetal growth disturbances. So, this indicator can serve as a marker of vascular inflammatory response (21). The most important finding in current study was the elevation of serum ferritin in case group than in control group with significant difference between both groups, this finding was in agreement with Kawilarang et al. 2019, who mentioned that significantly elevated level of serum ferritin as the risk factor in preterm labor (22). These findings were also in agreement with a study carried out by Shetkar NR et al. 2017, when they found a significant increase in mean serum ferritin in preterm labor women than those with full term (23). Moreover, it was in agreement with recent Iraqi study conducted at Al- Elwiyah Maternity Teaching Hospital, Baghdad, Iraq by Omran A and Sarsam S. 2021 that agreed with our finding in which there was highly significant increase of serum ferritin in preterm than in term labor (24). These findings were not in agreement with *Cekmez Y et al. 2015*, who found that serum level of ferritin can be used as a marker of preterm premature rupture of membranes (PPROM)but cannot be used as a marker for spontaneous preterm labor (25).The current study found that the mean serum albumin level was significantly decreased in case group than in control group. These findings were consistent with a study carried by *Heng Y et al*. 2015, who concluded that Albumin is significantly decreased in patients with spontaneous preterm delivery, they attributed that decrease of intracellular albumin to increase of cellular leukocytes (26). Moreover, these findings were in agreement with *Cetinkaya S et al* who reported that albumin was low among women with risk for preterm labor (16). These findings didn't match those observed by *Manzar S et al*. 2020, who mentioned that level of serum albumin was increased significantly in preterm

labor, this may be attributed to the difference in sample size collection between the studies (27). As our findings, *Keren-Politansky A et al. 2014*, found that the level of serum fibrinogen increased in preterm than term labor but also with no significant difference(28) while *Manesh H et al. 2020*, found that the level of serum calcium was decreased in preterm than in term labor but with no significant difference, these findings were consistent with those reported by (29) which were same as our results. The current study found that the validity test of serum ferritin to detect preterm labor at cutoff ≥ 52.7ng/ml) in case group as follows: Sensitivity (94%), specificity (90%), NPV (94%), PPV (90%) and the accuracy was (92%). These findings were in agreement with those found by *Omran A- Sarsam S et al. 2021*, as the validity test of serum ferritin to diagnose preterm labor showed that the sensitivity was (91.0%), specificity (95.0%), NPV (94.8%), PPV (68.0%) and the accuracy of the test was (93.0%) (24). These results were in line with Movahedi et al. 2012, study; where high ferritin considered as preterm labor predictor with (78.3% sensitivity) and (83% specificity)(30).

Conclusion

Elevated serum ferritin and decreased serum albumin in third trimester can be used for prediction of preterm labor. Thus; it is better to measure serum ferritin to all pregnant women in the third trimester with a risk of preterm labor.

Authors' contributions:

Dr. Maha Talib Mosa: writing the project, collecting data, writing draft, and research.

Dr. Wasan Wajdi: supervisor, concept of the study, reviewing manuscript

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دور متفاعلات الطور الحاد (الفرتين، الالبومين، الكالسيوم، الفايبرينوجين) في النساء الحوامل مع الولادة المبكرة

د. وسن وجدي /كلية الطب – جامعة بغداد/استشاري نسائية وتوليد/ مستشفى بغداد التعليمي
د. مها طالب موسى/ مستشفى بغداد التعليمي

الخلاصة:
خلفية الدراسة: الولادة المبكرة والخداجة المتعلقة بها لها عوامل مهيئة وبالتالي ازدياد معدل المراضة والوفيات في الفترة المحيطة بالولادة. متفاعلات الطور الحاد هي علامات التهاب التي تكون اما موجبة او سالبة تفسر بتفاعل المتفاعلات للاخماج التحت السريرية والتي تكون عادة مرتبطة مع الولادة المبكرة .
الهدف من الدراسة: تقييم دور متفاعلات الطور الحاد في النساء الحوامل مع الولادة المبكرة
المرضى والطريقة : دراسة الحالات والشواهد , أجريت في قسم النسائية في مستشفى بغداد التعليمي خلال الفترة من بداية شباط ،2021 إلى نهاية تشرين الاول، 2021 على مئة امرأة حامل خلال مدة الحمل من ٢٨ اسبوعا حتى ٣٦ اسبوع +٦ ايام. قسمت عينة الدراسة إلى مجموعتين: خمسون امرأة حامل مع الولادة التلقائية كمجموعة الحالة وخمسون امرأة مع عدم وجود علامات واعراض الولادة كمجموعة ضابطة. تم جمع العينة من النساء اللواتي زرن العيادة الاستشارية للمتابعة. تم سحب خمسة ملليلتر من الدم الوريدي لقياس نسبة سيروم (الفرتين، الالبومين ، الكالسيوم، الفايبرينوجين).
النتائج: متوسط نسبة الفيريتين في الدم في المجموعة الضابطة (46.2±16.2) (نانوغرام / مل) بينما في مجموعة الحالة (52.47± 11.6) (نانوغرام / مل) مع وجود فرق معنوي بين المجموعتين (ب=0.03)، متوسط ألبومين المصل في المجموعة الضابطة (3.18 ± 0.31) (جم / دل) بينما في مجموعة الحالة (2,92± 0.39) (جم / دل) مع معنوية عالية الفرق بين المجموعتين (ب=0.001). اختبار صلاحية مصل الفيريتين عند القطع ≤ 52.7 (نانوغرام / مل) في مجموعة الحالة على النحو التالي: الحساسية (94٪) ، النوعية (90٪) ، القيمة التنبؤية السلبية (94٪) ، القيمة التنبؤية الإيجابية (90٪) ، الدقة (٩٢%). اختبار صلاحية مصل الألبومين عند القطع ≤ 3.06 (جم / دل) في مجموعة الحالة على النحو التالي: الحساسية (78٪) ، النوعية (86٪) ، القيمة التنبؤية السلبية (78٪) ، القيمة التنبؤية الإيجابية (83٪) و كانت الدقة (٨٤%).
كان متوسط الفبرينوجين في المجموعة الضابطة (400.9 ± 38.1) بينما كان في مجموعة الحالة (410.7 ± 51.2) مع عدم وجود فرق معنوي بين المجموعتين (ب=0.1). كان متوسط الكالسيوم في الدم في المجموعة الضابطة (8.1 ± 0.7) بينما كان في مجموعة الحالة (7.92 ± 0.5) مع عدم وجود فرق معنوي بين المجموعتين (ب=0.1)
الاستنتاج: ارتفاع سيروم الفرتين، انخفاض سيروم الالبومين في الثلث الاخير من الحمل يستخدم للتنبؤ بالولادة المبكرة .
الكلمات المفتاحية: متفاعلات المرحلة، الحادة، الألبومين ، الفريتين ، الفيبرينوجين، الولادة المبكرة.