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Maternal Serum C-Reactive Protein for Prediction of Maternal and Perinatal Morbidity in Premature Rupture of Membranes

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ABSTRACT

Background: Premature rupture of membranes (PROM) is defined as spontaneous rupture of membranes before the onset of uterine contraction. If the rupture of the membranes occurs after 28 weeks but before 37 weeks of gestation it is termed as PPROM (Preterm Premature Rupture of Membranes).

Objective: To assess the role of the C- reactive protein (CRP) as a reliable predictor of chorioamnionitis in premature rupture of membranes (PROM).

Patients and methods: This is an observational prospective study that was conducted on 120 pregnant women admitted to Menoufia University Hospitals and Shebin EL-Kom Teaching Hospital during the period from October 2019 till December 2020.

Results: CRP level has sensitivity and specificity of (87.5% and 88.7%) respectively, at cutoff value >13 with area under curve of 0.915 with accuracy of 76.3% as the diagnostic tool in PPROM cases with histological chorioamnionitis (HCA). Also, C-reactive protein was significantly positively correlated with placental examination HCA, offensive discharge, ESR at 2nd hour, and TLC ($p<0.05$). Also, C-reactive protein was significantly negatively correlated with amniotic fluid index (AFI), Apgar score at (5, 10 minutes) and fetal weight at delivery ($p<0.05$). While, there was insignificant correlation between CRP with ESR at 1st hour among the studied patients ($P>0.05$).

Conclusion: CRP has a role for detection of maternal and perinatal morbidity with accuracy about 76% and can be used as an early predictor for morbidity in pregnant women with PPROM. Pregnant women with PPROM who had CRP level ≤13 mg/l should have expectant management if there are no other contraindications and those have CRP level >13 mg/l; termination of pregnancy should be taken in consideration in presence of signs of clinical chorioamnionitis.

Keywords: C-reactive protein, Perinatal, Premature, PROM, rupture of membranes.

INTRODUCTION

Premature rupture of membranes (PROM) is defined as spontaneous rupture of membranes before the onset of uterine contraction. If the rupture of the membranes occurs after 28 weeks but before 37 weeks of gestation it is termed as PPROM (Preterm Premature Rupture of Membrane). The incidence of PPROM is variable between 2-4.5% of all deliveries. It is responsible for 30% of preterm deliveries and contributes around 10% of perinatal mortality[(1)].

Microbial invasion of the amniotic cavity (MIAC) is identified in 30–40% of PPROM, particularly at early gestational ages acute chorioamnionitis (CAM) is a threat to both mother and fetus[(2)].

Signs of histological chorioamnionitis (HCA) are also observed after placental examination in up to 60% of all preterm deliveries[(3)]. Since expectant management of PPROM less than 34 weeks of gestational age is broadly recommended, the placental results cannot be correlated with amniotic fluid results due to the long latency between sampling and delivery[(4)].

Early infection is not reliably predicted by commonly used laboratory variables such as erythrocyte sedimentation rate, white blood cell count, neutrophil count or vaginal bacterial culture. Clinical signs such as fever and fetomaternal tachycardia usually appear. One of the markers in maternal serum, which indicates an increased risk of preterm delivery, is the C-reactive protein (CRP) [(5)].

CRP is being used in different parts of the world as early predictor of chorioamnionitis. Perinatal mortality after PPROM is most commonly associated with infection and prematurity, which leads to adverse neonatal outcomes as intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy and bronchopulmonary dysplasia [(6)].

Therefore, the aim of this study was to assess the role of the C-reactive protein (CRP) as a reliable predictor of chorioamnionitis in premature rupture of membranes (PROM).

PATIENTS AND METHODS

This is an observational prospective study that was conducted on 120 pregnant women admitted to Menoufia University Hospitals and Shebin EL-Kom Teaching Hospital during the period from October 2019 till December 2020.

Ethical consideration:

The study started after approval of protocol from Faculty of Medicine, Menoufia University, Ethical

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Committee for Human Research. For each patient included in the study the following procedure was done: Explanation of the importance of the study to the patients to become more interested and cooperative, the confidentiality of the patient's data was guaranteed, the patients had the right to refuse participation in this study without giving any reason and fully informed consent of volunteer was taken from the patients after explanation of the procedures.

All patients were selected according to inclusion and exclusion criteria as follow:

Inclusion criteria: Singleton pregnancy and premature rupture of membranes in pregnant women more than 28 weeks and less than 35 weeks.

Exclusion criteria: Pregnant women with respiratory infection at the time of admission, any long-standing diseases such as rheumatoid arthritis, patient with heart disease, diabetes, hypertension, preeclampsia or any complication and fetal congenital anomalies.

For every patient included in the study the following was done considering gestational age and uterine contractions:

Full detailed history: (personal history including name, age, sex, address, special habits of medical importance**,** complaint and present history**,** obstetric history like last menstrual period, gravidity and parity, history of previous abortion or ectopic pregnancies**,** estimation of expected delivery date and gestational age by Naegele's rule, history of previous PPROM or chorioamnionitis**,** menstrual history; age of menarche, last menstrual period, regularity of menstruation**,** contraception history, and detailed medical history was taken from each patient including special emphasis on medical and surgical history, history of drug intake and history of general disease e.g., diabetes mellitus.

Examination: (general examination and vital signs were measured daily (blood pressure, pulse, temperature, respiratory rate, abdominal examination for fundal level, fundal and pelvic grip and manual count of uterine contractions twice daily, obstetric examination: local vaginal examination and sterile speculum examination).

Full laboratory investigations: (CBC every 72 hours, ESR results every 48 hours, C-reactive protein levels: Maternal blood was collected prior to treatment with antibiotics, steroids and tocolysis. Maternal blood was obtained via venipuncture of the cubital vein at admission. Maternal serum CRP was measured using a high-sensitivity immunoturbidimetric analysis (Modular PP analyzer, Roche, Basel, Switzerland). CRP values were considered abnormal when the values exceed 6 mg/L) before delivery[7]**.** Duration and type of labor, mode of delivery and indication of operative delivery was recorded.

Assessment of fetal wellbeing: (Biophysical profile**:** twice weekly (ultrasound on pregnancy, AFI, Doppler on pregnancy) and cardiotocography (CTG) twice weekly.

Histopathological examination of placenta: was done for features of acute inflammation.

- Three blocks were taken from the placenta (peripheral, center and at the insertion of the umbilical cord).
- Sections was taken and stained with hematoxylin and eosin stain for grading and staging of inflammation.
- Histological chorioamnionitis was diagnosed by the presence of an unaltered neutrophil infiltration at the amniotic membrane and placenta (maternal inflammatory response), and at the umbilical cord «funisitis» (fetal inflammatory response) [8]**.**
- The term "stage" refers to the anatomical regions infiltrated by neutrophils, while the term "grade" refers to the intensity of the acute inflammation[9]**.**
- Regarding maternal inflammatory response staging and grading were scored as follows:
  - Stage 1: is characterized by the presence of neutrophils in the chorion or sub chorionic space.
  - Stage 2 refers to neutrophilic infiltration of the chorionic connective tissue and/or amnion, or the chorionic plate.
  - Stage 3 is necrotizing chorioamnionitis with degenerating neutrophils (karyorrhexis).
  - Grading: Grade 1 (mild to moderate) refers to individual or small clusters, diffusely infiltrating the chorion, chorionic plate, sub chorionic fibrin or amnion. Grade 2 (severe) consists of the presence of three or more chorionic microabscesses[9]**.**
- Regarding fetal inflammatory response: Staging: Inflammation of the umbilical vessels begins in the vein (phlebitis) (stage 1) and is followed by involvement of the arteries (arteritis) (stage 2), then infiltration of neutrophils into the Wharton's jelly (stage 3) [10]**.**

Neonatal outcome assessment: Apgar score at 5 and 10 mins after delivery**,** estimation of neonatal weight and recording neonatal admission to hospital or to neonatal intensive care unit (NICU) if happened and recording the duration of stay at hospital.

Statistical Analysis:

Our data were tabulated and analyzed statistically using MICROSOFT EXCEL 2019 and SPSS v. 21 (SPSS Inc., Chicago, IL, USA**)**. Statistical analysis was done using descriptive and analytical tests. Descriptive includes percentage (%), mean, standard deviation, range, and median. Analytical includes Chi-square (χ^2), Student t test (t), Mann-Whitney test (U), Kruskal Wallis test (K-W) and Pearson correlation (r). ROC curve (Receiver operator characteristic curve):

It is a graphic presentation of sensitivity against 1- specificity. It is done by comparing values of cases to detect a cutoff of certain outcome. Considering P-value < 0.05 statistically significant.

RESULTS

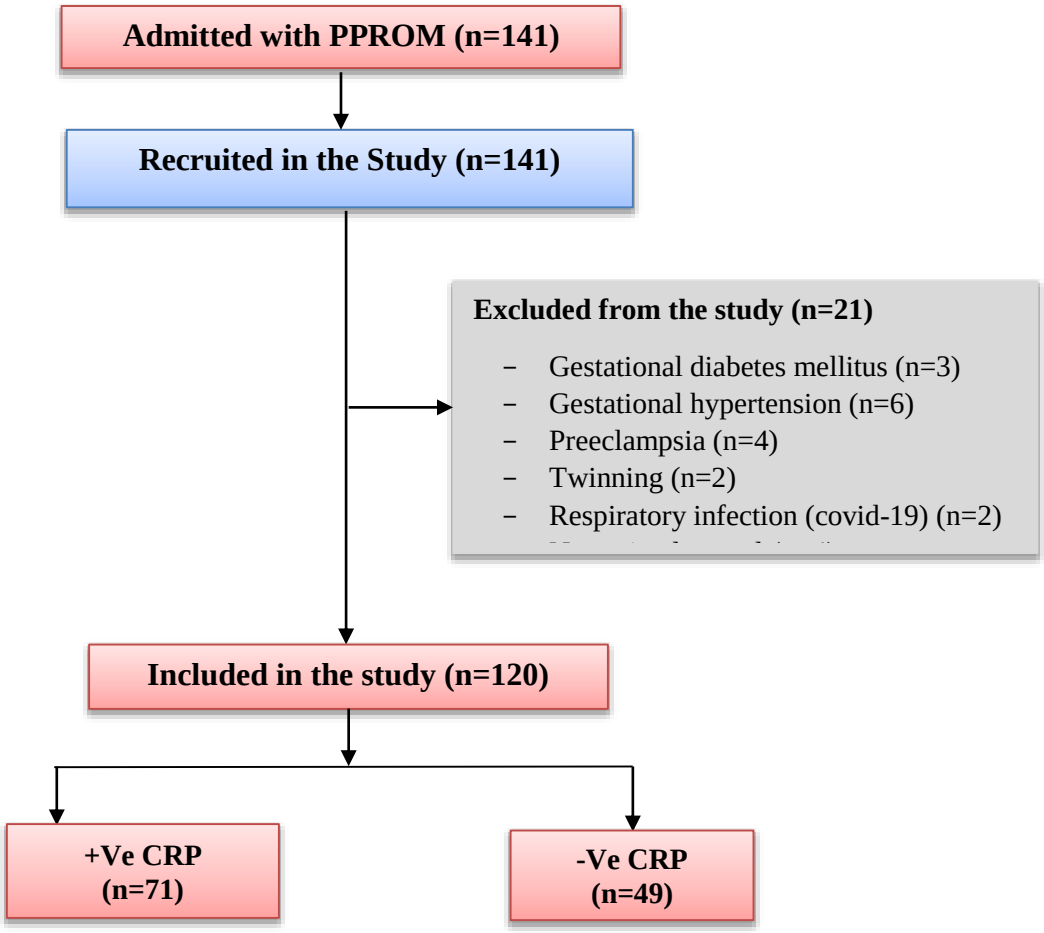

Fig. (1): Flowchart of the studied patients.

Demographic and historical data of the studied patients are shown in table 1.

Table (1): Demographic and historical data of the studied patients

Variables	Mean ±SD	Range	Median
Age (years)	26.45±4.88	19-38	20
Body Mass Index	28.53±2.97	23.11-34.67	26.40
Gestational age/weeks	33.45±1.36	28-35	33
	No.	%	
Previous PPROM			
No	94	78.33	
Previous PPROM	26	21.67	
Parity			
Nulli para	4	3.33	
P1	39	32.50	
P2	48	40.00	
P3	24	20.00	
>p3	5	4.17	
Previous CS			
No	37	30.83	
1 CS	34	28.33	
2 CS	35	29.17	
3 CS	14	11.67	
PPROM at gestational age (weeks)	33.45±1.38	28-35	32
Delivery at gestational age (weeks)	35.80±1.76	29-38	35

SD: Standard deviation, **PPROM:** Preterm premature rupture of the membranes, **CS:** Cesarean **section**

In our study, most of patients (27.50%) had spontaneous vaginal delivery, followed by (26.67) had CS due to drained liquor and previous CS. Also, 15.0% had elective CS because of previous CS (Table 2).

Table (2): Indications for termination of pregnancy (TOP).

Indications for termination of pregnancy	Total (n=120)	
	N	%
Cesarean section due to preterm labor previous cesarean section	14	11.67
Cesarean section due to placental abruption	6	5
Termination due to fetal distress and abnormal Doppler	7	5.83
Induction due to decreased amniotic fluid and high temperature	10	8.33
Elective cesarean section because of previous cesarean section	18	15.00
Cesarean section due to drained liquor and previous cesarean section	32	26.67
Spontaneous vaginal delivery	33	27.50

In our study, there was a significant association between maternal CRP with ESR at 2nd hour, TLC, pulse, temperature and offensive discharge among the studied patients. In our study, there was a high significant association between maternal CRP with amniotic fluid index (AFI) among the studied patients. In our study, there was significant difference between the studied groups regarding HCA for assessment of histological chorioamnionitis (Table 3).

Table (3): CRP in relation to clinical chorioamnionitis, amniotic fluid index and histological chorioamnionitis among the studied patients**.**

	C-reactive protein (CRP) (n=120)				P value
	Negative (n=49)		Positive (n=71)		
	Mean ±SD		Mean ±SD		
ESR 1st hour	28.23±4.21		49.19±4.13		0.924
ESR 2nd hour	52.45±3.79		96.96±6.30		<0.001**
TLC	8.08±2.64		10.39±3.19		0.016 *
Pulse	82.01±5.17		89.00±5.13		<0.001**
Temperature	37.24±0.23		37.74±0.66		<0.001**
	NO	**%**	**NO**	**%**	
Offensive discharge					<0.001**
• Present	2	4.08	25	35.2	
• Absent	47	95.92	46	64.8	
AFI					0.093
• 1>	1	2.04	5	7.04	
• 7>	7	14.29	19	26.76	
• ≥7	41	83.67	47	66.20	
HCA (placental examination)					<0.001**
• No	43	87.76	36	50.70	
• Acute inflammation	6	12.24	35	49.30	

ESR: Erythrocyte Sedimentation Rate, **SD:** standard deviation, **TLC**: Total leucocyte count, **AFI:** Amniotic fluid index **HCA:** Histological chorioamnionitis, *****significant ******highly significant

In our study, maternal CRP was significantly associated with Apgar score at 5 and 10 mins, fetal admission to hospital, fetal weight at delivery and duration of hospital stays among the studied patients (Table 4).

Table (4): CRP in relation to fetal outcomes.

	C-reactive protein (CRP) (n=120)				P value
	Negative (n=49)		Positive (n=71)		
	N	%	N	%	
Apgar score at 5 mins					
<7	16	32.65	48	67.61	<0.001**
≥7	33	67.35	23	32.39	
Apgar score at 10 mins					
<7	9	18.37	29	40.85	0.009*
≥7	40	81.63	42	59.15	
Fetal admission to hospital					
No	40	81.63	42	59.15	0.009*
Admitted	9	18.37	29	40.85	
Fetal weight/g at delivery					
<2000 g	1	2.04	11	15.49	0.010*
2000-2500 g	6	12.24	16	22.54	
>2500 g	42	85.71	44	61.97	
Duration of hospital stay/day Mean ±SD	7.00±1.05		6.62±3.42		<0.001**

SD: standard deviation, *****significant ******highly significant

In our study, there was a significant association between presence and absence of acute inflammation of HCA in cases of PPROM among the studied patients regarding ESR at 1st and 2nd hour, TLC, temperature, pulse, AFI and offensive discharge and (Table 5).

Table (5): HCA in relation to ESR, TLC, temperature, pulse, offensive discharge and amniotic fluid index among presence and absence of acute inflammation of HCA in cases of PPROM.

	HCA (n=120)				P value
	No (n=79)		Acute inflammation (n=41)		
	Mean ±SD		Mean ±SD		
ESR 1st hour	37.47±7.78		48.12±4.55		0.003*
ESR 2nd hour	75.96±2.59		87.37±9.03		0.037*
TLC	9.19±2.63		10.11±4.00		<0.001**
Temperature	37.43±0.42		37.77±0.77		<0.001**
Pulse	81.74±4.29		84.76±6.03		<0.002*
	N	%	N	%	P value
Offensive discharge					
• Present	4	8.86	23	48.78	<0.001**
• Absent	75	91.14	18	51.22	
AFI					
• 1>	0	0.00	6	14.63	<0.001**
• 7>	6	7.59	20	48.78	
• ≥7	73	92.41	15	36.59	

HCA: Histological chorioamnionitis, **ESR:** Erythrocyte Sedimentation Rate, **TLC:** Total leucocyte count **AFI:** Amniotic fluid index, **SD:** standard deviation, *****significant ******highly significant.

In our study, maternal CRP was significantly associated with maternal histological grade, maternal histological stage and fetal histologic stage among the studied patients (Table 6).

Table (6): CRP in relation to maternal histological grade, maternal histologic stage and fetal histologic stage.

Maternal histological grade	No.	C-reactive protein (CRP) levels		P value
		Mean ± SD	Min.-Max.	
Normal	79	7.05±5.50	2-33	<0.001**
Grade 1	25	19.82±10.04	4-37	
Grade 2	16	29.12±12.77	5-56	
Maternal histologic stage				
Normal	79	7.05±5.50	2-33	<0.001**
Stage 1	14	18.50±9.69	5-33	
Stage 2	17	24.14±10.79	4-49	
Stage 3	10	29.20±14.73	5-56	
Fetal histologic stage				
Normal	79	7.05±5.50	2-33	<0.001**
Stage 1	21	19.14±9.53	4-37	
Stage 2	14	27.67±11.49	5.5-49	
Stage 3	6	28.66±16.57	5-56	

SD: standard deviation, ******highly significant

In our study, CRP level had cutoff value >13 as the diagnostic tool in PPROM cases with HCA (Table 7).

Table (7): Cutoff of CRP level as the diagnostic tool in in PPROM cases with HCA.

	AUC	Cutoff	Sensitivity	Specificity	P value	95% CI	Accuracy
CRP level	0.915	>13.0	87.5%	88.7%	<0.0001**	0.850 to 0.958	76.3%

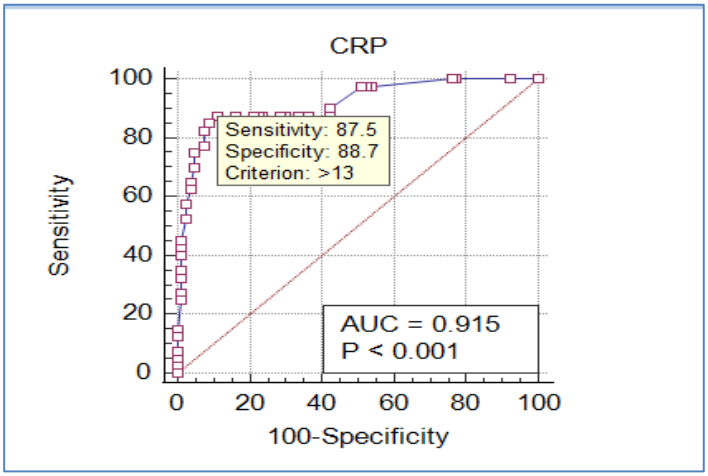

Fig. (2): ROC curve analysis of CRP level as the diagnostic tool in PPROM cases with HCA.

In our study, C-reactive protein was significantly positively correlated with HCA (placental examination), offensive discharge, ESR after 2nd hour, and TLC. Also, C-reactive protein was significantly negatively correlated with AFI, Apgar score at (5, 10 minutes) and fetal weight at delivery (Table 8).

Table (8): Correlation between C-reactive protein (CRP) and feto-maternal outcomes (Perinatal morbidity).

	C-reactive protein (CRP)	
	Correlation Coefficient	P value
HCA (placental examination)	0.450*	<0.001
AFI	-0.382*	0.012
offensive discharge	0.307**	<0.001
ESR 1st Hour	0.116	0.814
ESR 2nd Hour	0.617**	<0.001
TLC	0.501**	<0.001
Apgar score at 5 mins	-0.281**	0.002
Apgar score at 10 mins	-0.223*	0.017
Fetal weight at delivery	-0.354**	<0.001

HCA: Histological chorioamnionitis, **AFI:** Amniotic fluid index, **ESR:** Erythrocyte Sedimentation Rate, **TLC:** Total leucocyte count**.** The findings of histopathological examination of placenta are shown in figures 3 and 4.

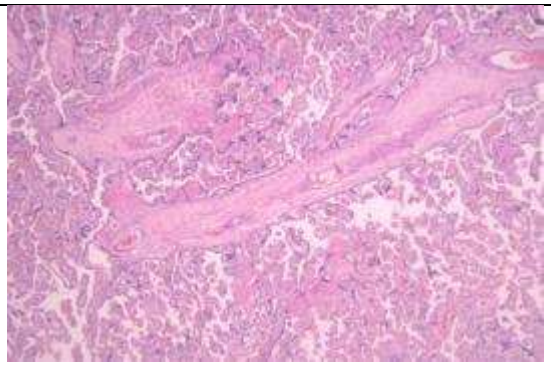

Fig. 3 a: Placental tissue composted of chorionic villi and fatal membranes with no histopathological evidence of chorioamnionitis (H and E x 40).

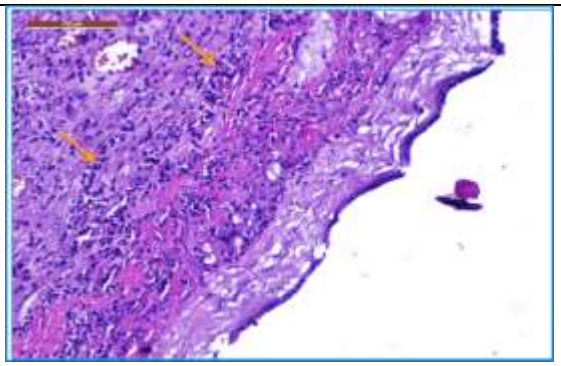

Fig. 3 b: Acute chorionitis is stage 1, grade 2. The neutrophilic infiltration is limited to the chorion (arrows), (H and E x 200).

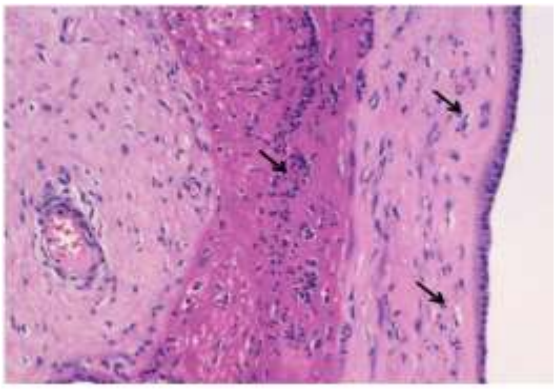

Fig. 3 c: Acute chorioamnionitis, stage 2, grade 1. The acute inflammation of the chorioamniotic membranes is seen reaching the amniotic connective tissue (black arrows (H and E x 200).

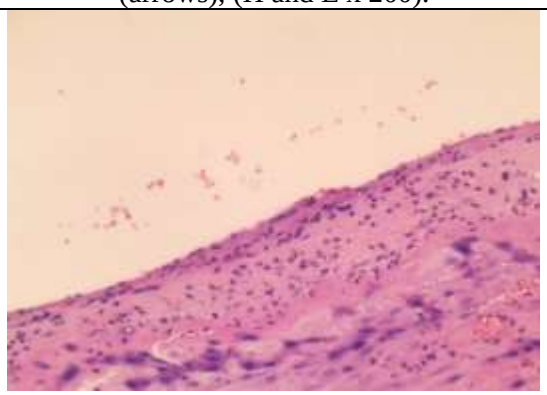

Fig. 3 d: Necrotizing chorioamnionitis is stage 3, grade 1. Acute inflammation of the chorioamniotic membranes, whose characteristic is the amnion epithelial necrosis (black arrows). Note also the associated fibrinoid necrosis the chorion (green arrows) (H and E x 200).

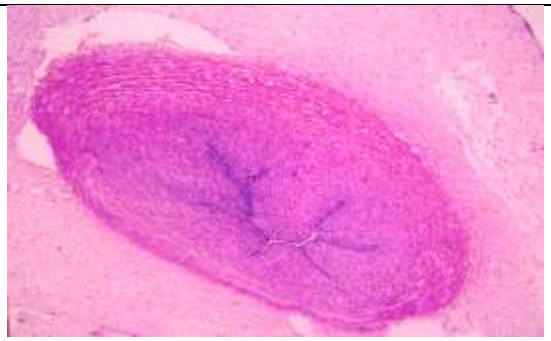

Fig. 4 a: section of umbilical vein showing inflammation (phlebitis) and edema (stage 1, fetal response), (H and E x 40).

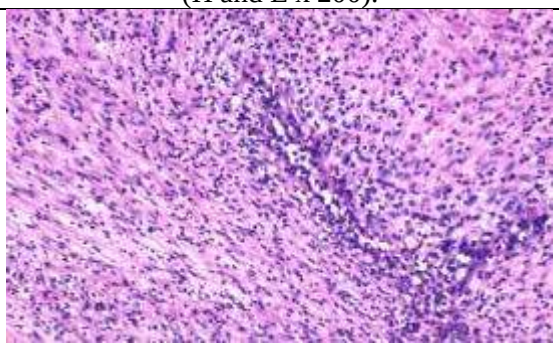

Fig. 4 b: Higher power view of previous section reveals dens neutrophilic infiltration of the umbilical vein (H and E x 200).

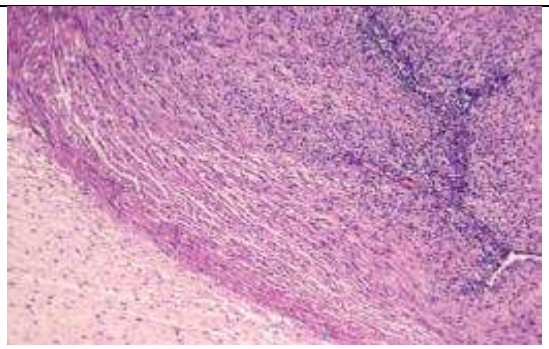

Fig. 4 c: Section of umbilical artery showing inflammation (arteritis) limited to the wall of the artery (stage 2, fetal response), (H and E x 200).

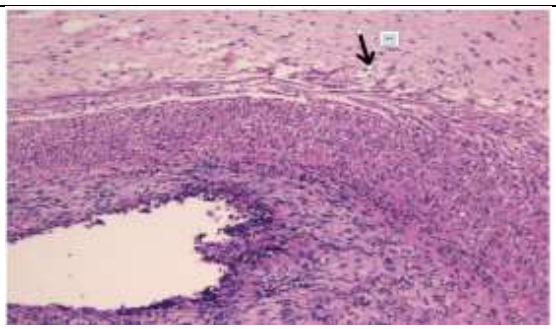

Fig. 4 d: Section of umbilical artery showing inflammation (arteritis) (stage 3, fetal response) associated with infiltration of neutrophils into the Wharton's jelly (arrow). (H and E x 200).

DISCUSSION

The current study showed that, there was a significant association between maternal CRP with ESR at 2nd hour, and TLC among the studied patients. While there was insignificant association between maternal CRP with ESR at 1st hour among the studied patients. This was consistent with **Naro *et al.* (11)** who showed a significant correlation between vaginal fluid CRP concentrations after PPROM and both amniotic fluid and umbilical cord CRP levels. The median vaginal fluid CRP concentration was higher in fetuses with funisitis, and the concentration >0.8 ng ml^{-1} remained a predictor of intra-amniotic infection and funisitis.

Our study showed that, maternal CRP showed significant association with Apgar score at 5 and 10 minutes, fetal admission to hospital, fetal weight/kg at delivery maternal, duration of hospital stays and histological chorioamnionitis (HCA) among the studied patients. In this line, **Fahmy *et al.* (12)** revealed that, the majority of delivered babies (54.79%) had an Apgar score <6 versus only (45.21%) had a score >6. Also, **Rawat *et al.* (13)** found Apgar score was >7 in 92% at 1 minute and in 94% at 5 minutes in PROM cases. Our findings agreed also with **Howman *et al.* (14)** who observed a significantly higher maternal inflammatory response when evaluating CRP in women with HCA. The high incidence of maternal and neonatal infection may be a consequence of decreased anti-bacterial activity in the amniotic fluid, which is low in early pregnancy and increases with gestational age. Another factor is the limited ability of the preterm infant to fight infection.

The present study revealed that, there was significant association between acute and non-acute inflammation of HCA among the studied patients regarding ESR, TLC, temperature, amniotic fluid index (AFI), and offensive discharge. Our findings agreed with **Naji and Seivani (15)** who indicated a significant correlation between maternal infection with histologic chorioamnionitis and the inflammatory indices of ESR, and PCT upon delivery. In line with our study, **Yoneda *et al.* (16)** found that the level of IL-8 in amniotic fluid and maternal body temperature were considered as the independent risk factors for chorioamnionitis.

The current findings revealed that, CRP level had sensitivity and specificity of (87.5% and 88.7%) respectively, at cutoff value >13 with area under curve of 0.915 with accuracy of 76.3% as the diagnostic tool in PPROM cases with HCA. This is consistent with studies by **Park *et al.* (17) and Hawrylyshyn *et al.* (18)** who suggested that CRP levels positively correlated with histopathological funisitis, and elevated levels indicated early-onset neonatal sepsis in patients with ruptured and unruptured membranes. Another study by **Lee *et al.* (19)** reported that sensitivity, specificity, positive prognostic value (PPV), and negative prognostic value (NPV) of an elevated serum CRP level (≥8 mg/L) were 74.1%, 67.5%, 32.8%, and 92.4% for funisitis and 67.7%, 63.3%, 17.2%, and 94.6% for early-onset neonatal sepsis (EONS), respectively. They concluded in their study that the maternal serum CRP level obtained up to 72 hour before delivery is a good predictor of funisitis and early onset neonatal sepsis (EONS) in women with preterm labor or preterm PROM. A low serum CRP level (<8 mg/L) has good NPV in excluding funisitis and EONS and may therefore be used as a noninvasive adjunct to clinical judgment to identify low-risk patients. Also, **Škrablin *et al.* (20)** showed significantly higher serum CRP levels in women who delivered newborns with congenital infection (20.5 versus 6.6 mg /L) and a value higher than 8.9 mg/L had 84% sensitivity and 69% specificity in prediction of neonatal sepsis.

Previous studies showed conflicting results with regard to the predictive value of CRP for maternal and fetal morbidity. Some authors demonstrated that CRP level was a poor predictor of infectious morbidity, and discouraged its routine use in PPROM **(21-25).** In addition, **Martius *et al.* (26)** showed a low prognostic value of maternal serum CRP measurements (cutoff>15mg/L).

CONCLUSION

Maternal CRP was significantly associated with Apgar score at 5 and 10 mins, fetal admission to hospital, fetal weight at delivery, maternal histological grade, maternal histological stage and fetal histologic stage and duration of hospital stay. CRP have a role for detection of maternal and perinatal morbidity with accuracy about 76% and can be used as an early predictor for morbidity in pregnant women with PPROM.

Pregnant women with PPROM who had CRP level ≤13 mg/l should have expectant management if there are no other contraindications and those have CRP level >13 mg/l, termination of pregnancy should be taken in consideration in presence of signs of clinical chorioamnionitis.

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