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Research Article

Role of Serum ferritin Level as an early predictor of Preterm Premature Rupture of Membranes.

Aliaa Shehata Mohamed[1], Moamen Mohamed Mohamed[1], Hashem Fares Mohamed[1] and Heba Hassan [1]

[1] Department of Obstetrics & Gynecology, Faculty of Medicine, Minia University, Egypt.

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Abstract

Background: Serum ferritin level and c_reactive protein act as an acute phase reactant may be elevated due to subacute genital tract infection leading to preterm premature rupture of membranes. **Aim and objectives:** To investigate whether serum ferritin level and crp can be utilized as a predictor of premature membrane rupture and chorioaminitis . **Research Design:** a case control study. **Subjects and methods:** case control research was performed in obstetrics and gynecology department, Minia university on 150 pregnant women with intact membrane for measuring the serum ferritin, CBC, CRP levels according to their age, parity, gestational age every 2 weeks (from 30 till 37 weeks). **Results:** Ferritin in all the 3 assessments was significantly increased in CRP positive cases when compared with CRP negative cases. Regarding comparison between CRP +ve and -ve cases, Age and Hb level were significantly increased in CRP +ve cases when compared with CRP -ve cases. There was significant positive correlation among S. Ferritin & CRP. **Conclusion:** The current research demonstrated that elevated serum ferritin and CRP levels are predictive of spontaneous preterm premature membrane rupture because they reflect an acute-phase response to subclinical infections. Preterm premature rupture of membranes was associated with substantially elevated serum ferritin levels, estimated by three distinct assessments.

Keywords: Preterm labor, Ferritin, Rupture of membrane.

Introduction

The medical condition known as preterm prelabor rupture of the membranes (pPROM) is characterised by the early rupture of the foetal membranes before reaching 37 weeks of gestation. This prevalent obstetric issue arises in approximately 3-4% of pregnancies and is closely associated with 40% to 50% of premature deliveries. Approximately 560,000 infants are delivered prematurely annually within the United States, accounting for approximately 12.0% of the overall number of births. Consequently, this data signifies a total of more than 150,000 instances of spontaneous preterm births (sPTBs) that are further worsened by preterm premature rupture of membranes (pPROM). In accordance with the findings of Kacerovsky et al., [1], the prevalence of preterm premature rupture of membranes (pPROM) surpasses that of preeclampsia, gestational diabetes, and other iatrogenic conditions that contribute to preterm birth. Additionally, there exists evidence indicating that the occurrence of infant mortality and morbidity is much greater within the subgroup of preterm births distinguished by preterm premature rupture of membranes (pPROM) as compared to other categories of preterm births. However, pPROM is a frequently overlooked and under studied disorder that has the potential to develop at any stage of pregnancy. Despite significant advancements in prenatal care over the last 30 years, there has been a concerning increase in the prevalence of preterm premature rupture of membranes (pPROM) and consequent preterm birth. The study conducted by Menon, Behnia, et al., [2] shown that many diagnostic techniques can be utilised for the retrospective diagnosis of preterm premature rupture of membranes (pPROM).

The therapy of individuals diagnosed with preterm premature rupture of membranes (PROM), irrespective of the gestational stage, is a subject of disagreement and divergence among healthcare practitioners. The choice of treatment strategy is contingent upon the gestational age of the individual and takes into account the possibility of childbirth in cases when the rupture of membranes occurs at or after 34 weeks of gestation. Numerous research studies have provided evidence supporting the efficacy of corticosteroid administration in reducing the occurrence of neonatal problems, particularly respiratory distress syndrome and intraventricular haemorrhage. Moreover, it has been established that the use of antibiotics has demonstrated effectiveness in prolonging the duration of the latency period. The ongoing scientific discussion is around the efficacy and appropriateness of tocolytic therapy and cervical cerclage, as indicated by the research conducted by Jahedbozorgan et al., [3] The advent of the COVID-19 pandemic has prompted scientists to engage in a further investigation of ferritin, thereby revitalising scholarly curiosity in this particular area of study. In contemporary times, the comprehension of ferritin extends beyond its conventional function as a mere indicator of iron levels. However, further investigation is required to obtain a full understanding of the precise function of ferritin, its impact on the development of inflammatory and autoimmune disorders, and its proinflammatory characteristics. A comprehensive comprehension of these facets will undeniably lead to advancements in the recognition, administration, and mitigation of potentially lethal consequences associated with diverse ailments.Based on the research conducted by Rasyid et al., [4]

Patients and Methods

Cross sectional research was performed in obstetrics and gynecology department, Minia university on 150 pregnant women with intact membranes for measuring the serum ferritin, CBC, CRP levels according to their age, parity, gestational age every 2 weeks (from 30 till 37 weeks) including the high-risk group for genital tract infection (multipara and low socioeconomic level increased maternal age).

The duration of the study was from November 2021 till September 2022.

Inclusion Criteria for study group: Pregnant women aged 20–45 years, Pregnant with intact membranes from 30 till 37 weeks of gestation, Hemoglobin (Hb) levels were ≥10.0gm/dl, and Highrisk pregnant women to genital tract infection (increased maternal age, multipara women and low socioeconomic level and those with previous history of preterm premature rupture of membranes are included .

Exclusion Criteria for groups: Medical disorders like severe anemia (hemoglobin <7 g/dl), gestational hypertension, pre-eclampsia and diabetes mellitus and Any suspected infectious diseases especially covid, malpresentation (breech, face) and multiple pregnancy.

Methods

Patients were subjected to: Complete history taking, Examination, Laboratory investigation (Complete blood picture (CBC), CRP and Serum ferritin (Human ferritin enzyme immunoassay test kit)).

Ethical Consideration: Study protocol had been submitted for approval by Institutional Review Board, Minia University. An approval of the Ethical Committee of Minia Faculty of Medicine was taken. Each participant in the research has provided informed written permission. Confidentiality and personal privacy were protected at all stages of the research .

Ethical code: MUEOB00080

Data management and Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage , quantitative continues group represent by mean ± SD , the following tests were used to test differences for significance;., correlation by Pearson's correlation or Spearman's . P value was set at <0.05 for significant results & <0.001 for high significant result.

Data were collected and submitted to statistical analysis. The following statistical tests and parameters were used.

Results

Table (1): Demographic data of included subjects

Parameter	Value (N = 100)
Age (Years)	25.13 ± 4.87
BMI (Kg/m2)	28.05 ± 2.75
Gestational age (Weeks)	31.65 ± 1.1
NormalVaginalDelivery	19 (19%)
Socioeconomic level	
• **Low**	63 (63%)
• **Moderate**	37 (37%)
Education	
• **High**	12 (12%)
• **Primary**	9 (9%)
• **Secondary**	63 (63%)
• **illeutriet**	16 (16%)
Occupation	
• **Housewife**	97 (97%)
• **Working**	3 (3%)
Residence	
• **Rural**	90 (90%)
• **Urban**	10 (10%)

Body mass index (BMI), Normal Vaginal Delivery (NVD)

This table showed the average body mass index (BMI) of the subjects is 28.05 kg/m2, with a standard deviation of 2.75. The average gestational age of the subjects is 31.65 weeks, with a standard deviation of 1.1. Out of the total participants, 19 individuals (19%) had a normal vaginal delivery (NVD). The average number of previous scars among the subjects is 1.86, with a standard deviation of 0.84. The majority of the subjects (63%) belong to a low socioeconomic level, while 37% are classified as having a moderate socioeconomic level. Among the subjects, 12% have a high level of education, while 9% have only primary education. The majority (63%) have secondary education, and 16% have no formal education. A large majority of the subjects (97%) are housewives, while only 3% are employed. Regarding residence about 90% lived in rural areas and 10% were urbans

Table (2): Initial Lab investigations of included subjects

Parameter	Value (N = 100)
Hb level (g/dl)	10.94 ± 0.76
S. Ferritin	87.34 ± 174.9
TLC per cubic mm	10650 ± 3838.6

This table showed that Mean Hb level was 10.94 (g/dl) with SD of 0.76. Mean S. Ferritin level was 87.34 with SD of 174.9. Mean TLC was 10650 per cubic mm with SD of 3838.6.

N.B. CRP +ve cases only who undergo rupture of membranes.

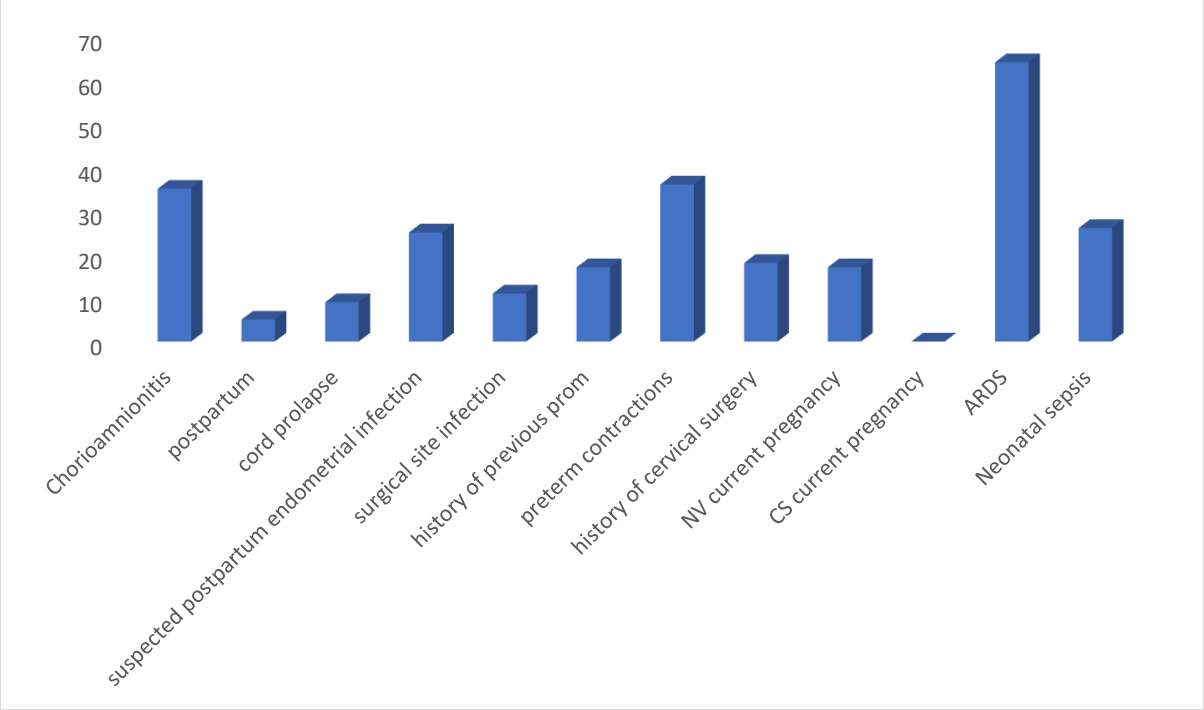


Figure (1): Maternal and Fetal complications among included subjects
N.B: postpartum= postpartum hemorrage.

Table (3): Comparison between CRP +ve and -v cases.

	CRP +ve	CRP -ve	P. Value
Age	26.51 ± 4.77	24.3 ± 4.78	0.028073*
Gestational age	31.59 ± 1.04	31.69 ± 1.15	0.685219
History of previous abortions	0.62 ± 0.83	0.72 ± 1.14	0.645163
Parity	1.76 ± 1.48	1.38 ± 1.34	0.194966
Gravity	3.08 ± 2.15	2.77 ± 2.46	0.527176
• **Hgb level 1st**	11.14 ± 0.91	10.82 ± 0.64	0.046868*
• **Hgb level 2nd**	10.48 ± 0.57	10.29 ± 0.43	0.31384
• **Hgb level 3rd**	10.26 ± 0.34	10.15 ± 0.29	<0.0001

This table showed that Regarding comparison between CRP +ve and -ve cases, Age and Hb level were significantly increased in CRP +ve cases when contrasted with CRP -ve cases.

Table (4): Comparison between CRP +ve & -v cases regarding S. Ferritin levels

	CRP +ve	CRP -ve	P. Value
S. Ferritin 1st	141.55 ± 218.97	19.35 ± 5.88	0.00332*
S. Ferritin 2nd	145.57 ± 189.38	27.23 ± 8.08	0.00094*
S. Ferritin 3rd	163.7 ± 190.84	40.93 ± 10.79	0.00068*

This table showed that S. Ferritin in all the 3 assessments was significantly increased in CRP positive cases when compared with CRP negative cases.

Table (5): Correlation between S. Ferritin and different parameters

	S. Ferritin 1st Assessment		S. Ferritin 2nd Assessment		S. Ferritin 3rd Assessment	
	R	P. Value	R	P. Value	R	P. Value
Age	0.089015	0.378478	0.098199	0.331053	0.102757	0.30899
Gestational age	-0.07034	0.486809	-0.06726	0.50612	-0.06849	0.498373
History of previous abortions	0.158007	0.116395	0.153047	0.128461	0.151436	0.13258
Parity	0.17855	0.075509	0.183611	0.067458	0.190196	0.05804
Gravity	0.18697	0.062512	0.188294	0.060643	0.191376	0.056473
Hb level	-0.12762	0.208102	-0.12033	0.235478	-0.11925	0.23974
CRP	.316**	0.001377	.326**	0.000941	.334**	0.000677
CRP level	.484**	0.00002	.484**	0.00002	.486**	0.00002

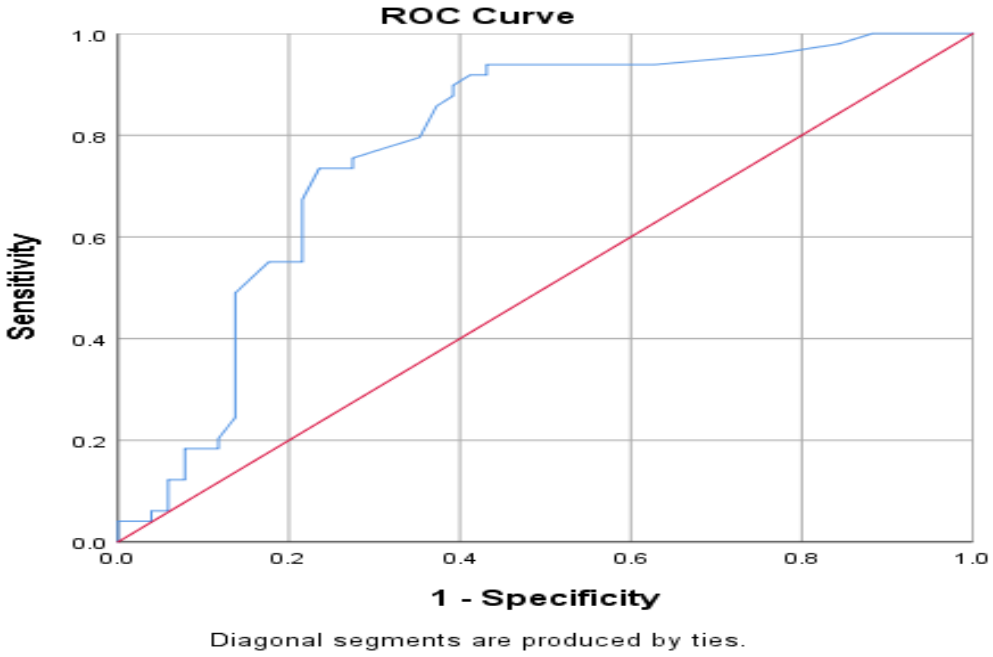
r: Pearson Correlation

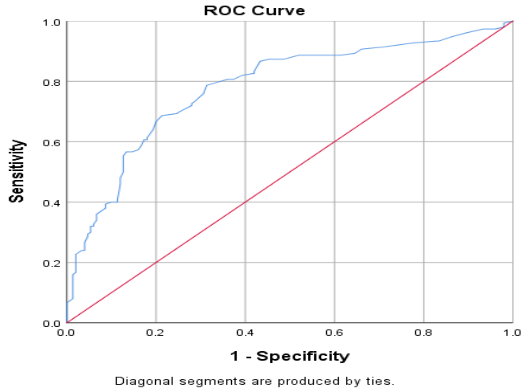
This table showed that there was significant positive correlation among S. Ferritin and CRP.

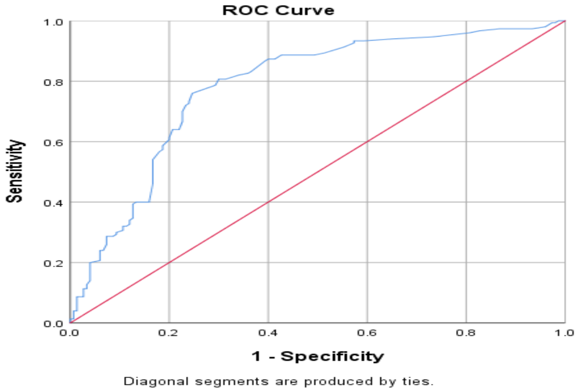
Table (6): ROC curve analysis of S. Ferritin and CRP positivity

Cutoff	AUC	Sensitivity	Specificity	P. Value
17.5	0.778	98%	84.3%	<0.0001*

This table showed that with cutoff value 17.5 there was significant association between s. ferritin and CRP as sensitivity reached 98% and specificity was 84.3%.




ROC Curve
Sensitivity
1 - Specificity
Diagonal segments are produced by ties.


ROC Curve
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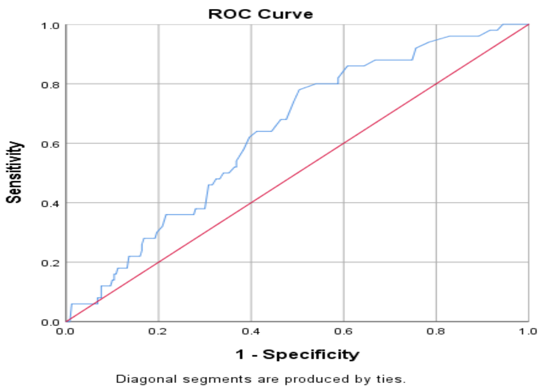
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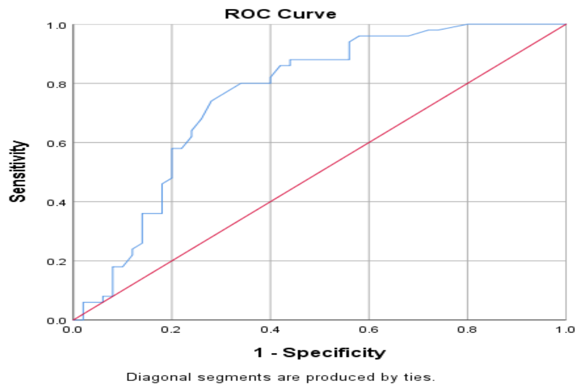
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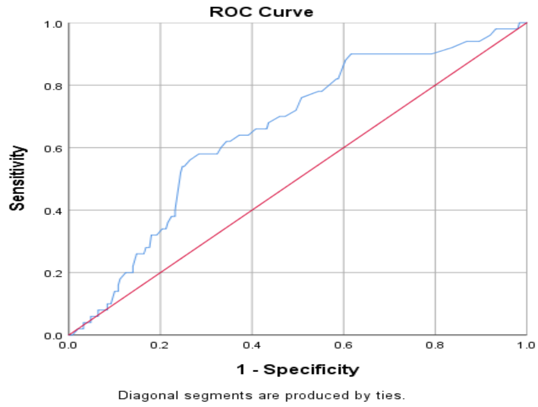
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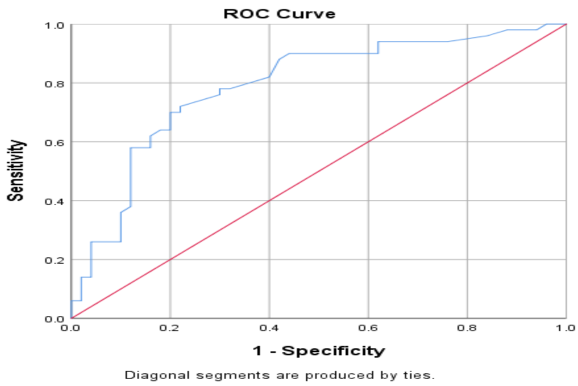
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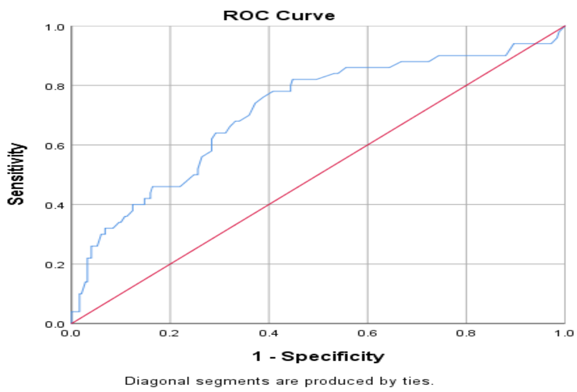
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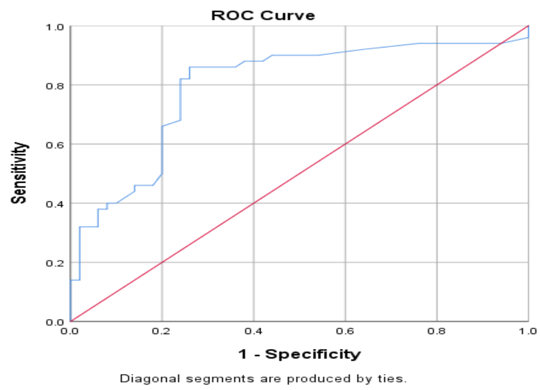
ROC Curve
Sensitivity
1 - Specificity
Diagonal segments are produced by ties.

Discussion

The main findings of this study were as follows:

In relation to the demographic characteristics of the list being studied, it was found that the average age of the participants in the research was 25.13 years, with a standard deviation of 4.87 .

In a study conducted by Pezzilli et al., a sample of 50 individuals diagnosed with PROM was recruited. The study's participants had an average age of 26.70±4.The study's results indicated that those who were diagnosed with premature rupture of membranes (PROM) had a significantly lower average age of 19 years compared to those with intact membranes. [5] In addition, the study conducted by Poon et al., revealed a significant association between maternal age and a heightened probability of encountering spontaneous early preterm premature rupture of membranes (PPROM).[6]

In contrast, Baumfeld et al., have demonstrated that there exists no significant correlation amongst maternal age and the prediction of preterm premature rupture of membranes (PPROM). [7]

Based on the findings of the current research, it can be inferred that the mean gestational age (GA) was 31.65, with a standard deviation (SD) of 1.1. The findings from the analysis indicated that there was a prevalence incidence of 19% for normal vaginal delivery.

However, the new investigation indicates a significantly diminished value. Jia et al., did a study in China which revealed a predilection for vaginal delivery as opposed to caesarean section (CS) delivery among patients diagnosed with premature rupture of membranes (PROM). Based on the results of the investigation, there was a notable rise in the percentage of individuals opting for vaginal delivery, with a statistically significant increase observed from 68.9% in 2012 (P<0.001) to 76.5% in 2014 (P<0.001). However, this proportion subsequently declined to 69.3% in 2017 (P<0.001).[8] Moreover, Ademi Ibishi et al., reported that the prevalence of caesarean section in the aforementioned study was seen to be 28% among persons who were diagnosed with premature rupture of membranes (PROM). [9]

The present investigation revealed that the C-reactive protein (CRP) yielded favorable results in 38% of the examined cases, with an average value of 16.54. Therefore, the findings of this study indicate a potential correlation between increased levels of C-reactive protein (CRP) and the incidence of preterm premature rupture of membranes (PROM).

The research conducted by Hazra et al., yielded findings that support the utilization of C-reactive protein (CRP) as a dependable and expeditious diagnostic indicator for histological chorioam-nionitis. The results of the study revealed that C-reactive protein (CRP) exhibited a sensitivity rate of 100% and a specificity rate of 50%. The research revealed that the positive predictive value was 29.27%, whilst the negative predictive value was 100%. In contrast, the sensitivity rate of the total leukocyte count (TLC) was found to be just 37.93%. Therefore, the inclusion of C-reactive protein (CRP) as a biomarker holds considerable importance in the detection of early and subclinical infections, which can potentially play a role in the initiation of preterm labor and premature rupture of membranes. [10]

Furthermore, Mehndiratta et al., presented empirical data suggesting that 31% of persons who received a diagnosis of premature rupture of membranes (PROM) exhibited a positive outcome in relation to their C-reactive protein (CRP) levels. The study additionally shown that maternal C-reactive protein (CRP) had a sensitivity of 83.33% and a specificity of 80.76%. The findings of the study indicated that the sensitivity and specificity of white blood cell count in the identification of intra-amniotic infection were determined to be 64.86% and 58.73%, respectively. The researchers have concluded that C-reactive protein (CRP) is a more dependable diagnostic indicator than white blood cell (WBC) count for predicting intra-amniotic infection in pregnancies with premature rupture of membranes. [11]

In relation to the comparison between persons who demonstrate positive C-reactive protein (CRP) findings and those who exhibit negative CRP findings, significant increases in age, hemoglobin (Hb) levels, and serum ferritin levels were observed among the CRP positive

patients as opposed to the CRP negative instances.
Based on the findings presented in the research conducted by Ramakrishnan et al., a notable association was observed between serum ferritin and CRP levels (r 0.06, P=0.006) in individuals diagnosed with PROM. [12]

In contrast to the findings obtained in the present investigation, Park et al.,(28) revealed a lack of statistical significance in the relationship between Intra-Amniotic Infection/Inflammation and maternal age among persons diagnosed with PROM.
The findings of this study indicate that the average haemoglobin (Hb) content was 10.94 g/dl, accompanied by a standard deviation (SD) of 0.76. The mean serum ferritin concentration was determined to be 87.34, accompanied with a standard deviation of 174.9.
The results of the study revealed that individuals who were diagnosed with premature rupture of membranes (PROM) demonstrated increased concentrations of S. Ferritin.

The elevated levels of ferritin in the circulatory system observed in cases of preterm premature rupture of membranes (PPROM) may be attributed to the concurrent presence of infection in individuals with PPROM. The present study aims to offer a full comprehension of the mechanisms implicated in the inflammatory response, ultimately resulting in the deterioration of cellular membranes. Several investigations have been conducted to determine the prevalence of infection-induced preterm premature rupture of membranes (PPROM) (29, 30).
The study conducted by Leslie et al., provides empirical evidence that supports the proposition that preterm premature rupture of membranes is associated with elevated levels of serum ferritin, when compared to a control group. The identified discrepancies were found to be statistically significant.[13]

The findings of this study are consistent with the research conducted by Mills et al., which reported a statistically significant elevation in blood ferritin levels among individuals experie-ncing preterm labor. Moreover, recent findings have unveiled that the optimal approach to reducing the occurrence of preterm birth is timely identification of pregnant individuals who fall into the high-risk category. [14]

The rise in blood ferritin levels found in persons with preterm premature rupture of membranes (PPROM) is indicative of an "acute phase reaction" that is likely initiated by a subclinical infection or inflammation in the vaginal region. The potential utilization of serum ferritin as an indicator for preterm premature rupture of membranes (PPROM) has been suggested, presenting medical professionals with the possi-bility of predicting the onset of this illness. [15]

Vaginocervical infections are more prone to arise during pregnancy as a result of changes in vaginal pH. After the establishment of bacterial colonization, macrophages migrate to the chorion-decidual interface, leading to the production of ferritin as a response to acute phase reactants. According to the findings of there was a notable rise in serum ferritin levels observed in individuals who experienced preterm birth. An increase in incidences has been noted during the intermediate phase of gestation. The significant potential of serum ferritin levels to serve as a predictive indicator for spontaneous preterm delivery, particularly in cases occurring during the early stages of gestation, is deserving of attention. [16]

Conclusion

The findings of this study indicate that increased levels of serum ferritin and CRP can serve as prognostic markers for spontaneous preterm premature rupture of membranes and chorioa-minits. These raised levels are indicative of an acute-phase response to subclinical infection.

Outcome Measures:
Primary outcome:
Elevation of serum ferritin level predicted and decreased the incidence of preterm premature rupture of membrane and decreased its adverse effects on the mother from infection (chorioa-minitis), preterm labor abruptioplacenta and also prevented prematurity of fetus, include fetal/ neonatal infection, respiratory disorders such as pulmonary hemorrhage, broncho-pulmonary dysplasia, chronic lung disease, perinatal asphyxia, fetal distress and patent ductus arteriosus. Neurological complications

include intraventricular hemorrhage, cerebral palsy and periventricular leukomalacia.

Secondary outcome:
During pregnancy, pregnant women need to have a reasonable diet and rest, supplement with adequate nutrients and shouldn't smokeitis necessary to transfer pregnant women to a level with allow birth weight preterm infant care unit for social care and monitoring.

Recommendations:
The current study also revealed that here was significant positive correlation between S. Ferritin and CRP in preterm premature rupture of membrane. The current study was limited by small sample size, the lack of control group, being a single center study and relatively short follow up period. Further controlled studies with larger sample size and longer follow-up are needed to confirm our results and to identify risk factors of poor outcome.

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