SJIF IMPACT FACTOR: 5.79 CRDEEP Journals
International Journal of Life Sciences Omar et. al., Vol. 7 No. 4 ISSN: 2277-193x
International Journal of Life Sciences. Vol. 7 No. 4. 2018. Pp. 115-119

Full Length Research Paper

Serum Ferritin as a Marker for Preterm Premature Rupture of Membranes

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Article history
Received: 25-07-2018
Revised: 28-07-2018
Accepted: 31-07-2018

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Abstract
Objectives: *The present study determine whether serum ferritin levels could be used as a predictive marker of spontaneous preterm premature rupture of membranes or not.* ***Methods:*** *This study was conducted on pregnant females (30-37 weeks). Serum iron was low among group I when compared with group II (P=0.04) and high among group II when compared with group III (P=0.004).* ***Conclusion:*** *Serum ferritin acts as a marker for preterm premature rupture of membranes and could be used to expect complications by obstetricians and it considered more specific for prediction.*

Keywords*: Preterm labor, Ferritin, Rupture of membrane.*

Introduction

Preterm delivery is associated with substantial short as well as long term psychological, emotional, physical or financial impacts. Preterm labor means delivery before thirty-seven completed weeks of gestational age of pregnancy. About 15 million new born were born preterm and the number is increasing. Premature rupture of membranes occurs in 3% of pregnancies and considered the main cause of one third of preterm deliveries (WHO, 2014). Preterm premature rupture of membranes (PPROM) means spontaneous rupture of fetal membranes before 37 completed weeks and before the onset of labor (Cunningham et al., 2014). More than 50% of women diagnosed with PPROM, delivery occurred within one week of membrane rupture. Pregnancy after rupture of membranes was inversely associated with the gestational age at the time of membrane rupture. PPROM also associated with Intra-amniotic infection (13–60%) and placental abruption (4–12%). These complications occur more frequently at earlier gestational age of rupture (Mercer, 2003). The severity and frequency of associated neonatal complications increases when the gestational age at diagnosis decreases. Respiratory distress syndrome is the most common serious complication observed in babies after a pregnancy complicated by PPROM (American College of Obstetrics and Gynecology, 2013).

Necrotizing enterocolitis, contractures (associated with long-standing oligohydramnios), Intraventricular hemorrhage, sepsis, umbilical cord prolapse (especially when the fetal presentation is non-vertex) and also cesarean delivery for malpresentation considered the most significant neonatal complications associated with PPROM. Severe anhydramnios or oligohydramnios increases the incidence of umbilical cord compression and non-reassuring fetal testing, which increase cesarean delivery rate. The presence of intra-amniotic infection or inflammation with PPROM associated with raised neurodevelopmental delay rate (Yoon et al., 2000). Maternal complications are typically secondary to the increased likelihood of infection associated with PPROM. Intra-amniotic infection in patients with PROM is significantly higher for those with preterm PROM (13–60%) compared to those with PROM at term (1%) (Packard and Mackeen, 2015).

Treatment depending on gestational age and includes consideration of delivery when rupture of membranes occurs at or after 34 weeks' gestation. Corticosteroids decreases neonatal complications, especially respiratory distress syndrome and intraventricular hemorrhage and antibiotics are effective for increasing the latency period (Medina and Hill, 2006). Ferritin is a protein found inside cells that stores iron, so your body can use it later. A ferritin test indirectly measures the amount of iron in the blood. Serum ferritin level in the blood is directly related to the amount of iron stored in the body. Ferritin is an acute phase reactant as it increases during inflammation. The high level of ferritin is most likely a part of acute phase reaction to subclinical genital tract infection or inflammation. It can be used as a marker for PPROM and may help the physicians to anticipate it (Beck et al., 2002). It has been proposed that extracellular ferritin has an important role in host defense against bacteremia by stimulating oxidative metabolism. Some mechanisms have been suggested for these evidences. First, the presence of increased levels of ferritin might reflect an acute phase reaction to subclinical genital tract infection or inflammation. In addition, it may be also explained by the covert process of infection associated with preterm delivery that causes tissue damage resulting in increased serum ferritin levels that act as an acute phase reactant (Nandini et al., 2015). So, the aim of our study was to determine the effect of serum ferritin levels in prediction of spontaneous preterm premature rupture of membranes.

Patients and Methods

The present case control study was conducted at Obstetrics and Gynecology department of AL-Azhar University hospital (New Damietta) during the period from April 2016 to December 2017. It included three groups; Group I: 70 women with spontaneous

preterm labor, group II: 70 women presented with preterm premature rupture of membranes not in labor and group III: 70 women at the same gestational age with no risk of spontaneous preterm labor with intact membrane as a control group. This study participated after oral and informed consent with the following criteria: women with gestational age from 30 weeks to 37 weeks with premature rupture of membranes, women with gestational age from 30 weeks to 37 weeks with spontaneous preterm labor pain and pregnant women with no risk for preterm labor pain or PPROM. All of the following criteria were excluded; anemia (Hb equal or less than 10 gm / dl), iron overload state, pre-existing chronic infective disease, multiple pregnancy, polyhydramnios, genital tract infections, malignancy, chronic diseases (liver & kidney) and possible causes of iatrogenic preterm labor as antepartum hemorrhage, pre-eclampsia, etc.

Methodology

Patients eligible for the study was underwent the following: full history, complete examination including general, abdominal and pelvic examination. Investigations including; trans-abdominal and transvaginal ultrasound were done.

Study design

Under complete aseptic conditions 4 ml of peripheral venous blood were withdrawn from the antecubital vein using disposable plastic syringe after sterilization of skin with iso propyle alcohol (70%) swabs obtained from each women in all groups. 1 ml blood added to heparinized tube for determination of hemoglobin levels (Srivastava et al., 2014) and the remaining 3 ml blood collected in disposable plastic tubes and blood left to clot and then centrifuged at 3000 rate per minute to separate serum which was kept in Eppendorf tube at -20°C until time of assay of serum ferritin (Nandini et al., 2015) and serum iron (Garcic, 1979).

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using statistical package for social sciences (SPSS) version 19 (SPSS Inc, Chicago, USA), running on IBM compatible computer . Quantitative data were expressed as the mean ± standard deviation (SD). Qualitative data were presented as relative frequency and percent distribution. For comparison between two groups, the independent samples (t) test or Mann-Whitney tests were used. For comparison between categorical groups, the Chi square (X2) or Fisher's exact tests were used. Pearson correlation co-efficient (r-test) was used for correlating different variables. For all tests, P values < 0.05 were considered significant. For all tests, P values > 0.05 were considered insignificant.

Results

The present cross-sectional study included 210 women, 70 women with spontaneous preterm labor, 70 women presented with preterm premature rupture of membranes not in labor and 70 women at the same gestational age period with no risk of spontaneous preterm labor and with intact membranes. Age, BMI and parity were nearly comparable with non-statistical significant difference between the studied groups (table 1). The hemoglobin level was nearly comparable with non-statistical significant difference between studied groups. The serum ferritin level was high among group II and group III when compared with group I and low among group III when compared with group II with statistical significant difference. Level of serum iron was high among group II when compared with group I and low among group III when compared with group II with statistical significant difference (Table 2).

Table (1): Comparison between demographic data of the studied groups

Variable	Group I (n= 70)	Group II (n= 70)	Group III (n= 70)
Age (years)			
Mean± SD	27.2 ± 2.48	26.2 ± 2.5	26.8 ± 1.7
Range	22-31	21-29	24-29
BMI (Kg/m^2)			
Mean± SD	30.2 ± 1.3	29.4 ± 0.86	29.1 ± 1.39
Range	28.4-32	28-31	26-30.8
Parity			
Mean± SD	1.5 ± 0.97	1.4 ± 1.1	1.3 ± 0.9
Range	0-3	0-3	0-3

Group I: *Women at the same gestational age with no risk of spontaneous preterm labor with intact membrane;* ***Group II:*** *Preterm premature rupture of membranes not in labor;* ***Group III:*** *Spontaneous preterm labor.*

Table (2): Comparison between laboratory data of the studied groups.

Variable	Group I (n= 70)	Group II (n= 70)	Group III (N = 70)
Hemoglobin level (mg/dl)			
Mean± SD	10.82 ± 0.55	10.51 ± 0.83	10.52 ± 0.66
Range	9.9-11.7	9.4-11.9	9.8-12
Serum ferritin (microgram/L)			
Mean± SD	29.2 ± 6.6*	42.8 ± 7.5*	35.8 ± 3.4 *#
Range	21-37	31-55	30-40
Serum iron level			

(microgram/L)	110.0 ± 12.47	128.5 ± 12.55*	116.6 ± 12.01#
Mean± SD	90-130	100-141	99-130
Range			

**: significant compared to group I; # significant compared to group II.*
Group I: *Women at the same gestational age with no risk of spontaneous preterm labor with intact membrane.* ***Group II:*** *Preterm premature ruptures of membranes not in labor.* ***Group III:*** *Spontaneous preterm labor.*

The serum ferritin levels in this study are more sensitive to predict preterm labor and PPROM **(table 3).**

Table (3): Sensitivity, specificity, positive and negative likelihood ratio and positive and negative predictive values of group II and III.

Parameter	**Percentage ratio**	
	Group II	**Group III**
Sensitivity	91.84%	91.49%
Specificity	90.20 %	86.79 %
Positive Likelihood Ratio	9.37	6.93
Negative Likelihood Ratio	0.09	0.10
Positive Predictive Value	90.00%.	86.00%
Negative Predictive Value	92.00%	92.00 %

Group II: *Preterm premature rupture of membranes not in labor****; Group III:*** *Spontaneous preterm labor.*

Discussion

This study aims to determine whether serum ferritin levels could be used as a predictive marker of spontaneous preterm premature rupture of membranes or not. In the present study, there were no-statistically significant differences between three groups regarding BMI and parity. Khambalia et al. (2015) found that being overweight or slightly obese was not associated with the overall risk of preterm birth. These results agree with Kim et al. (2011) and Palatnik and Grobman (2015) who reported that the mean age and BMI was not different between the study and the control group, and also, in agreement with Yael et al., (2015) who noticed that maternal age had no significant difference of prediction of preterm labor. In contradiction, Greco et al. (2011) noticed that the risk for spontaneous early preterm delivery increases with maternal age. Kim et al. (2011) reported that parity not significantly difference between study and control group. Fernandes and Chandra (2015) reported that the risk of preterm labor increased with parity.

In the present work, the hemoglobin level was nearly comparable with non-statistical significant difference between the studied groups. Khambalia et al. (2015) reported that there is some evidence of a U-shaped relationship between hemoglobin concentrations in early pregnancy and the risk of preterm birth. In Singapore, analysis of 3728 deliveries was done. It was observed that anemic women have high incidence/risk of preterm delivery at the time of delivery than non-anemic. No other difference in neonatal outcome was observed (Manzoor et al., 2015). Older women are at greater risk of preterm birth and still birth (Lisonkova et al., 2010). Studies carried out in UK, France and USA showed that grand multiparity and nulliparity were associated with increased rate of preterm labor (Manzoor et al., 2015). On the other hand, Ulmer and Joepel (1988) studied the hematological values included hemoglobin level, serum iron and serum ferritin in 300 pregnant women. They found only the determination of serum ferritin is of particular relevance as a significant correlation was ascertained between low serum ferritin levels and the incidence of preterm labor.

In the present study, the serum ferritin level was high among preterm labor and preterm premature rupture of membrane when compared with control group with statistically significant differences. These results agree with Siddika et al. (2009) and Nandini et al. (2015) showed serum ferritin levels were significantly higher in preterm labor. The best and most effective prevention of preterm delivery incidence is early identification of pregnant women who belong to a group of high risk (Nandini et al., 2015). Pregnancy predispose to vaginocervical infection due to altered vaginal pH. The chorion-decidual interface is infiltrated by macrophages following bacterial colonization and ferritin is produced as an acute phase reactant (Paternoster et al., 2002). A study done by Saha et al. (2000) noticed that significantly high levels of serum ferritin in patients who had preterm delivery. It seems that elevated mid-pregnancy serum ferritin levels can be predictive of spontaneous preterm delivery, especially those occurring at early gestational ages.

Some mechanisms have been suggested for these evidences. First, the presence of increased levels of ferritin might reflect an acute phase reaction to subclinical genital tract infection or inflammation (Ramsey et al., 2002). In addition, it may be also explained by the covert process of infection associated with preterm delivery that causes tissue damage resulting in increased serum ferritin levels that act as an acute phase reactant (Goel et al., 2003). Another study showed that a serum ferritin level higher than 41.5 ng/mL at 28 weeks increased the risk of having a preterm delivery nine-fold (Chen et al., 2006). A retrospective study by Gopal et al. (1988) had shown no relation between serum ferritin levels and spontaneous preterm labor. Even though there is widespread suspicion that subclinical infection is a common accompaniment and cause of spontaneous preterm labor, serum ferritin levels was not significantly raised in group of spontaneous preterm labor cases. So it shows spontaneous preterm labor may be due to multifactorial causes than attributing only to subclinical infection (Valappil et al., 2015). A study conducted by Goncalves et al. (2002) showed that microorganisms are not recovered from the amniotic fluid in all women with spontaneous preterm labor, the incidence of positive cultures in women with spontaneous preterm labor averages only 15%. Since the serum

ferritin levels are not significantly raised, it cannot be used a marker of spontaneous preterm labor. In the present study, the serum iron level was high among preterm premature rupture of membrane when compared with control one with statistically significant differences. These results in agree with Valappil et al. (2015) who reported that there was no significant statistical difference in the mean iron values of women with PPROM and spontaneous preterm labor when compared to the control group. The lack of significant statistical difference may be due to the wide range in serum iron levels and day to day variations in serum iron. Serum iron values in an individual can vary within a single day or from day to day (Dale et al., 2002).

Conclusion

Elevated serum ferritin level is predictive of early spontaneous preterm premature rupture of membrane because it reflects an acute- phase reaction to subclinical infections. Serum ferritin was significantly elevated in preterm premature rupture of membranes when compared to the control group of women with same gestational period. Serum ferritin acts as a marker for preterm premature rupture of membranes and could be used to expect complications by obstetricians and it considered more specific for prediction**.**

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