Significance of Maternal Serum Ferritin in case of Preterm Labor

Thesis

Submitted for Partial Fulfillment of Master Degree

in ***Obstetrics and Gynecology***

By

Noha El Enany Mohamed

(M.B.,B.Ch., Ain Shams University)

Resident of Obstetrics and Gynecology

Quesna General Hospital, Menoufiya

Under Supervision of

Prof. Dr. Bahaa Abdel Kader Fateen

Professor of Obstetrics and Gynecology

Faculty of Medicine – Ain Shams University

Dr. Amr Mohamed El Helaly

Lecturer of Obstetrics and Gynecology

Faculty of Medicine – Ain Shams University

Faculty of Medicine

Ain Shams University

List of Contents

Title	Page

- **Introduction and Aim of the Work 1**
- **Review of Literature:**
  - **Chapter 1:**
    - **Preterm Labor 4**
      - **Definition and Incidence 4**
      - **Risk Factors for Preterm Labor 6**
      - **Pathogenesis of Preterm Birth 19**
      - **Tests for Prediction of Preterm Labor and Delivery 25**
      - **Management of Preterm Labor 37**
  - **Chapter 2:**
    - **Ferritin 46**
- **Patients and Methods 63**
- **Results 72**
- **Discussion 85**
- **Conclusion and Recommendations 94**
- **Summary 95**
- **References 98**
- **Arabic Summary ..... --**

List of Figures

Fig. No	Subjects	Page

Review

1. Part of 1 24-subunit model of a ferritin molecule showing iron-core crystalline adhering in random orientations to the inner protein surface..... 55
2. Diffuse x-ray pattern of the ferritin micelle in cubic crystals 56
3. Model of ferritin showing probable subunit arrangement (24 subunits at apices of a snub cube). The iron core (shown dark) can be seen through the inner subunit spaces 56

Results

1. Comparison between group I (preterm labor group) and group II (full term labor group) as regards age 73
2. Comparison between group I (preterm labor group) and group II (full term labor group) as regards parity 75
3. Comparison between group I (preterm labor group) and group II (full term labor group) as regards Hb concentration 77
4. Comparison between group I (preterm labor group) and group II (full term labor group) as regards serum ferritin level..... 78
5. Relation between serum ferritin in the two groups and the parity 80

List of Tables

Tab. No	Subjects	Page
	Review	
1.	Risk of recurrent preterm birth in a third pregnancy	7
2.	Risk of preterm birth with selected infections	15
3.	Risk of preterm delivery	26
	Results	
1.	Comparison between group I (preterm labor group) and group II (full term labor group) as regards age	72
2.	Comparison between group I (preterm labor group) and group II (full term labor group) as regards parity	74
3.	Comparison between group I (preterm labor group) and group II (full term labor group) as regards Hb concentration	76
4.	Comparison between group I (preterm labor group) and group II (full term labor group) as regards serum ferritin level	78
5.	Relation between serum ferritin in the two groups and the parity	79
6.	Relation between serum ferritin level in the two groups as regard age and gestational age	81
7.	The cutoff value of serum ferritin between group I, II.	82
8.	Maternal characteristics of preterm labor (group I) and the control (group II) full term in labor as regard different variables	84

List of Abbreviations

ACTH ..... **Adrenocorticotropic hormone**
BV ..... **Bacterial vaginosis**
CRH ..... **Corticotropin releasing hormone**
CRP ..... **C-reactive protein**
CS ..... **Corticosteroids**
DHEA-S ..... **Dehydroepiandro-sterone sulfate**
ELBW ..... **Extremely low birth weight**
ELISA ..... **Enzyme linked immunosorbent assay**
FFN ..... **Fetal fibronectin**
Hb ..... **Hemoglobin**
HCG ..... **Human chorionic gonadotropin**
HPA ..... **Hypothalamic-pituitary adrenal**
HPAaxis ..... **Hypothalamic-pituitary adrenal axis**
IUGR ..... **Intrauterine growth retardation**
LBW ..... **Low birth weight**
NSAID ..... **Non steroidal anti-inflammatory drugs**
PG ..... **Primigravida**
PPROM ..... **Preterm premature rupture of membranes**
PROM ..... **Premature rupture of membranes**
PTB ..... **Preterm birth**
PTD ..... **Preterm delivery**
PTL ..... **Preterm labor**
RDS ..... **Respiratory distress syndrome**
SGA ..... **Small for gestational age**
SIDS ..... **Sudden infant death syndrome**
TNF ..... **Tumor necrosis factor**
VLBW ..... **Very low birth weight**

Acknowledgments

First and above all, my deepest gratitude and thanks to **God** *for achieving any work in my life.*

I would like to express my especial cordial thanks, endless gratitude and appreciation to **Prof. Bahaa Abdel Kader Fateen,** *Professor of obstetrics and Gynecology, Faculty of Medicine, Ain Shams University for giving me the opportunity to work under his meticulous supervision. His honest assistance and patience make me truly indebted to him.*

With great pleasure I am also grateful to **Dr. Amr Mohamed El Helaly,** *Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his kind effort and support that made achievement of this work possible. God bless him for precious time and efforts given to me in this work.*

Lastly I would like to thank my family for their support given to me to complete this work.

Introduction

Preterm delivery is a major problem in obstetrics, complicating 8–12% of all births and responsible for 70–85% of perinatal mortality and for approximately 50% of long-term morbidity. In about half of the cases, the cause of preterm delivery is not known. However, accumulating evidence suggests that subclinical intrauterine infection with unknown etiology may be responsible for the majority of cases ***(Romero et al., 2002)***

Preterm labor was defined as regular uterine contractions in patients before 37 completed weeks of gestation with intact membranes with 4cm or more of cervical dilatation observable during a 2-hours period ***(Saha et al., 2000).***

Although the pathophysiology of preterm delivery remains largely unknown, efforts have been made to try and identify clinical, bacteriological and biochemical markers that could predict preterm labor. One such protein is ferritin, an iron storage protein, that when increased is considered to be an acute phase reactant during inflammation ***(Adi et al., 2005).***

Ferritin provides the primary form of iron storage in the body. Since the first demonstration of a relationship between: serum Ferritin concentration and the level of iron stores there have been many subsequent studies of this relationship. The possible role of Ferritin during inflammation has recently been demonstrated. It has been proposed that extracellular ferritin has an important role in host defense against bacteremia by stimulating oxidative metabolism ***(Worwood, 1982).***

A large proportion of early spontaneous preterm deliveries is associated with upper genital tract infections and most patients show little or no sign of infection. The authors undertook this study to examine the relationship between preterm delivery and serum ferritin as a possible marker of infection ***(Gibbs et al., 1992).***

Aim of the Work

The aim of this study is to compare the serum ferritin levels in women with preterm labor (PTL) with those women full term in labor.

Preterm Labor

Definition:

Preterm delivery refers to birth between the onset of viability and 37 completed weeks gestation ***(Steers, 2005).***

Preterm birth (PTB) refers to a birth that occurs before 37 completed weeks of gestation. A very PTB is more variably defined as less than 32, 33, or 34 weeks of gestation, and an extremely preterm birth is a birth at less than 28 weeks of gestation ***(Caughey, 2008).***

Prematurely born infants also are classified by birth weight. Infants who weigh less than 2500 g, 1500 g, and 1000 g are defined as low (LBW), very low (VLBW), and extremely low birth weight (ELBW). Not all LBW infants are premature, some are small for gestational age (SGA) while others are both premature and SGA ***(Caughey, 2008).***

Incidence:

In developed countries 12.7 percent of births in 2005 occurred preterm; 2.03 percent of all births were less than 32 weeks of gestation and 9.1 percent of all births were from 34 to 36 weeks of gestation ***(Goldenberg et al., 2008).***

This reflects 20 percent rise in the overall proportion of PTBs since 1990.

Preterm birth is also a major determinant of short - and long-term morbidity in infants and children ***(Lockwood et al., 1993).***

The risk for these morbidities is directly related to the gestational age and birth weight. Short-term morbidities associated with preterm delivery include respiratory distress syndrome, intraventricular hemorrhage, peri-ventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and patent ductus arteriosus. Long-term morbidities include cerebral palsy, mental retardation, and retinopathy of prematurity ***(Goldenberg et al., 2008).***

The major reason for the increase in PTB is a higher rate of multiple gestation: between 1996 and 2002 the multiple birth ratio increased over 20 percent to 33 per 1000 live births (twin birth rate: 31/1 000).

Pregnancies complicated by multiple gestation are prone to PTB; approximately 50 percent of twins and 90 percent of triplets are born preterm compare to less than 10 percent of singletons ***(Martin et al., 2002).***

Changes in obstetrical management (e.g., expanded use of ultrasound and induction of labor for abnormal findings), patient sociodemographic factors (e.g., more births at advanced maternal ages), and patient behavioral characteristics may have also contributed to the increase in PTB ***(Joseph et al., 1998).***

Risk Factors for Preterm Labor:

Identification of risk factors for preterm birth (PTB) before conception or early in pregnancy ideally would lead to interventions that could help to prevent this complication ***(Robinson, 2008).***

The many risk factors associated with spontaneous preterm labor and delivery may be classified as permanent or reversible.

Reproductive Factors:

History of preterm birth:

Some risk factors for PTB likely persist from pregnancy to pregnancy. Prior PTB is the strongest risk factor for future PTB, although most women who have had a PTB will have subsequent pregnancies of a normal duration ***(Ananth et al., 2006).***

Recurrences often occur at the same gestational age. The risk of PTB is highest when:

- The previous PTB was in the penultimate pregnancy.
- There is a history of multiple PTBs.
- The previous PTB occurred, before 28 weeks of gestation ***(McManemy et al., 2007).***

After three PTBs less than 35 weeks of gestation, the risk of a fourth PTB before 35 weeks is 67%. The risk of recurrent periviable delivery is of particular concern, given its high morbidity and mortality. Although an increased risk of recurrence exists, the recurrence risk appears to be lower than in women with later preterm births ***(Bloom et al., 2001).***

Table (1): Risk of recurrent preterm birth in a third pregnancy.

Obstetrical history	**Risk of PTB (percent)**
Two prior preterm births	42%
Both at 32 to 36 weeks	33%
Both at less than 32 weeks	57%
Term birth followed by PTB	21%
PTB followed by term birth	13%
Two prior term births	5%
PTB: preterm birth	

(McManemy et al., 2007)

Induced abortion:

Older studies suggested there was no increased risk, but subsequent studies have been less reassuring. Recent studies suggest an association between induced abortion and preterm labor ***(Moreau et al., 2005).***

Delayed ovulation:

Gestational age estimation by early ultrasound examination that is at least seven days less than that determined by menstrual dates is suggestive of a prolonged follicular phase of the menstrual cycle (i.e., late ovulation). Such a discrepancy was associated with an increased risk of PTB ***(Gardosi et al., 2000).***

Short interpregnancy interval: Short interpregnancy intervals have been reported as a risk factor for PTB in some studies ***(Robinson et al., 2008).***

Genotype:

The risk of PTB and increased risk of recurrent PTB appears to be due, in part, to genetic factors. Genetic susceptibility to PTB is suggested by the observation that PTBs are more prevalent in some family pedigrees and racial groups. One possible mechanism is that maternal and fetal genotypes in these cohorts may affect the mother's or fetus response to environmental factors and thus increase the risk of preterm delivery ***(Annells et al., 2004).***

A mother who is born preterm is at no or minimally increased risk of preterm delivery in her own pregnancies. Male infant gender is also a risk factor for spontaneous preterm birth. Two studies reported placental histology associated with male preterm infants was more likely to show signs of chronic

inflammation than that associated with female preterm infants. The hypothesis is that this may represent a maternal immune reaction to fetal tissue and that this response was more prominent when the fetus was male ***(Goldenberg et al., 2006).***

Assisted reproductive: Pregnancies conceived with assisted reproductive technologies are at higher risk of preterm birth ***(Robinson et al., 2008).***

Multifetal gestation: Multiple pregnancy accounts for 2 to 3% percent of all births, but 17% of all births less than 37 weeks of gestation. The incidence of multiple gestation has increased as ART using superovulation and in vitro fertilizatioin has become widely available and successful in achieving pregnancy ***(Kiely et al., 1998).***

The mechanism for preterm labor in multiple gestations, and particularly higher order multiple gestations, may be related to uterine distension, increased intrauterine volume, or related complications such as cervical incompetence. Multiple gestations produce a proportionately increased amount of estrogen, progesterone, and sex steroids compared to singleton pregnancies. Increased steroid production in multiple pregnancies may play a role in initiation of preterm labor. In particular, higher circulating levels of relaxin associated with super-ovulation may cause cervical incompetence, with subsequent PTB ***(Weiss et al., 1993).***

Prior multifetal gestation: Whether PTB of twins is associated with an increased risk of PTB in a subsequent singleton pregnancy is unclear ***(Facco et al., 2007).***