Serum amyloid A level in women with primary un explained early recurrent pregnancy loss

Thesis

Submitted for the partial fulfillment of Master Degree in Obstetrics andGynecology

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2014

Acknowledgment

First of all, all gratitude is due to ***Allah*** *for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

Really I can hardly find the words to express my gratitude to ***Prof. Dr. Ahmed ramy mohammed ramy*** *Professor of Obstetrics and Gynecology, for his supervision, continuous help, encouragement throughout this work and great effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.*

I am also grateful to ***Dr.Mostafa Ibrahim Ibrahim,*** *Assistant Professor of Obstetrics and Gynecology for his guidance, continuous assistance and sincere supervision of this work.*

I would like also to express my sincere appreciation and gratitude to ***Dr.Ahmed sheriff abdu elhamed*** *lecturer of Obstetrics and Gynecology , for his continuous directions and support throughout the whole work.*

Last but not least, I dedicate this work to my family,my husband ,my daughter kater elnada ,and my son mohammed, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

AMNA OMAR ALSHWARF

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Ward abbreviation

Ward abbreviation	Title
RPL	Recurrent pregnancy loss
SAA	Serum amyloid A level
HLA	Human leucocyte antigen.
NK	Natural killer cells.
USPC	Uterine serous papillary carcinoma.
ICSI	Intra cytoplasmic sperm injection.
NVD	Normal vaginal delivery.
P1C/S	Previous one cesarean section.

Introduction

Recurrent pregnancy loss (RPL) is defined by the Americansociety for reproductive medicine as the presence of two or more failed pregnancies, proved either by sonographic examination orhistopathology **(Fertility and Sterility, 2008).**

RPL is one of the most common obstetrical complications.

RPL may be either a primary or secondary process:

primary RPLrefers to those women with RPL who never had a live birth before**(Ansari et al., 1998,Paukku et al.,1999).**

Where as secondary RPL is occurrence of two or moreconsecutive spontaneous miscarriage after previous viablepregnancy**(Ansari et al., 1998).**

Multiple etiologies, such as endocrine, anatomic, genetic, hematological and immunological causes have been reported for thisdevastating disease. However, Over half of the cases remainunexplained .Thrombotic/inflammatory processes are often observedat the maternal-fetal interface as the final pathological assault in many cases of RPL, including those of unexplained etiologies)**(Kwak et al.,2009,Donckers et al.,2012).**

Serum amyloid A (SAA) is a highly conserved, acute-phaseprotein synthesized mainly by the liver. After secretion into thecirculation, it associates with high-density lipoprotein (HDL) molecules. During acute inflammation, serum SAA levels mayincrease up to 1000-fold, and under these conditions, SAA displacesapolipoprotein A-I from HDL, thus becoming the

majorapolipoprotein of circulating HDL3. SAA exhibits significant immunological activity by, for example, inducing the synthesis ofseveral cytokines and by being chemotactic for neutrophils and mastcells. It performs many of its immunological activities by bindingand activating cell-surface receptors, including Toll-like receptor(TLR) 2 and TLR4, formyl peptide receptor-like 1 (FPRL1), class Bscavenger receptor CD36, and the ATP receptor P2X7. SAA alsorecently has been shown to catalyze the inflammatory cascade,which has a key role in immune activation, thus further stressing thespecial role of SAA in immunomodulation**(Eklund et al ., 2012).**

Traditionally, SAA has been considered to have a major rolein the pathogenesis of amyloid A-type amyloidosis, but we nowunderstand that it may also participate in the pathogenesis of chronicinflammatory disorders , such as rheumatoid arthritis and atherosclerosis. Recently ,investigators found that elevated serumamyloid A is associated with venous thromboembolism**(Eklund et al ., 2012,Deguchi et al., 2013).**

Marked increase of SAA level in preeclampsia ,and their interrelation,may at least in part contribute to the pathogenesis ofpreeclampsia .To the best of our knowledge currently, there is nopublished data about th maternal SAA levels of patients with RPL**(Engin et al.,2007).**

Aim ofthework

The aim of the current study is to evaluate levels of serum amyloid A level in blood samples from patients with primary un-explained recurrent pregnancy loss.

Chapter (1):Recurrent pregnancy loss

Introduction;-

The medical terminology applied to women's experiences during early pregnancy has changed over time. Before the 1980s, health professionals used the phrase "spontaneous abortion" for a miscarriage.***(Moscrop et al., 2013).***

Miscarriage is the accepted formal term for early pregnancy loss before fetal viability***(Farquharson et al., 2005),*** those born before 24 weeks of gestation rarely survive***.(Mohangooet al.,2013).***

Definition of recurrent pregnancy loss:-

The American society for reproductive medicine defines (RPL)as ;two or more failed pregnancies (documented by ultrasound or histo-pathological examination) and suggests some assessment after each loss with a thorough evaluation after three or more losses ***(ASRM, 2008).***

Historical analysis of the medical terminology applied to early pregnancy loss in Britain has shown that the use of "miscarriage" (instead of "spontaneous abortion") by doctors only occurred after changes in legislation (in the 1960s) and developments in ultrasound technology (in the early 1980s) allowed them to identify miscarriages***(Moscrop et al., 2013).***

Incidence:-

As previously recurrent miscarriage (RM)is officially defined as three consecutive pregnancy losses less than 24 weeks of gestation.It

represented that the observed incidence of(RM)(0.5%-1%) is higher than the calculated risk(0.35%),based on a miscarriage risk of 15%

From there it can be concluded that there is a sub group of patients with higher miscarriage risk ***(Exalto et al., 2005).***

Epidemiological studies suggest that the risk of subsequent pregnancy loss is approximately 24%after two clinical pregnancy losses,30%after three,40%after four consecutive spontaneous abortion ***(Pandey et al., 2005).***

Subgroups of recurrent miscarriage:-

Based on the pregnancy history, three different groups of women with recurrent miscarriage can be identified, and the risk of subsequent miscarriage among these groups varies***(Daya, 2000).***

(I) Primary recurrent miscarriage group:

This group consists of women with three or more consecutive miscarriages with no pregnancy progressing beyond 20weeks gestation.

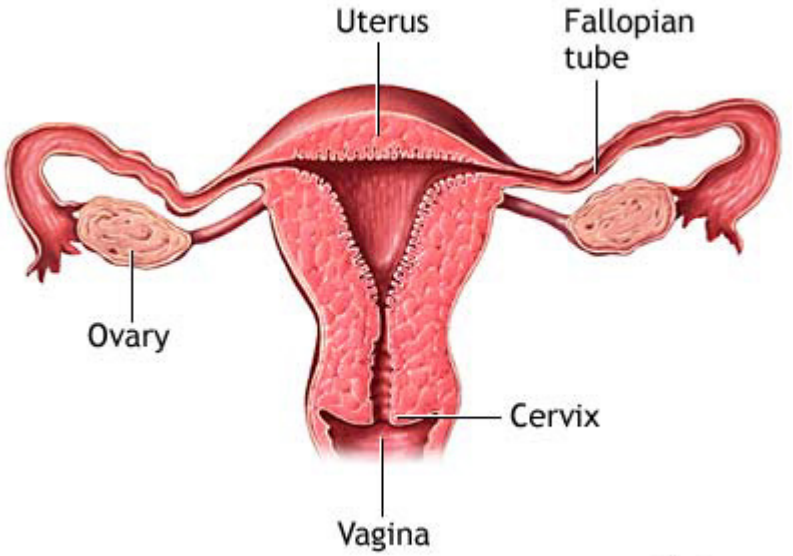
(II) Secondary recurrent miscarriage group:

This group consists of women who have had three or more miscarriages following at least one pregnancy that has gone beyond 20 weeks gestation, and may have ended in live birth stillbirth, or neonatal death.

(III)Tertiary recurrent miscarriage group***:***

This group has not been well studied and consists of women who have had at least three miscarriages that are not consecutive but are interspersed with pregnancies that have progressed beyond 20 weeks gestation (and may have ended in live birth, stillbirth, or neonatal death).

The current approach of lumping all three groups together makes it difficult to make recommendations regarding optimal evaluation and management***((Daya, 2000).***



Causes:-

1.Anatomical conditions:

A-Uterine conditions:-

uterine malformation is considered to cause about 15% of recurrent miscarriages***(ACOG,2008);-***

- **Uterine müllerian anomalies;-**

The most common uterine defects include septate, unicornuate, bicornuate, and didelphic uteri. Of these, the unicornuate uterus is least common. The highest rate of reproductive losses are found in bicornuate uteri (47%) compared with unicornuate uteri (17%), but both are frequently associated with second trimester loss and preterm delivery. Women with unicornuate and didelphys uteri have the highest rate of abnormal deliveries, while women with uterine septa have a 26% risk of reproductive loss***(Homer et al., 2000).***

- **septate uterus;-**

Theseptate uterus is the uterine anomaly associated with the poorest reproductive outcome and the most common uterine abnormality associated with RPL,the longer the septum is the worse the prognosis***(Homer et al., 2000,Proctor et al., 2003).***

The mechanism by which a septate uterus causes pregnancy loss is not clearly understood, but poor blood supply to the septum leading to poor implantation is one possibility***(Buttram,et al., 1979).***

- **Leiomyoma;-** Submucousleiomyomas that protrude into the endometrial cavity can impede normal implantation as a result oftheir position.An association between pregnancy loss and intramural or subserousmyomas is less clear, having been demonstrated in some, but not all studies***(Simpson,2007).***
- **Endometrial polyps ;-**

There have been no data showing a relationship between endometrial polyps and RPL ,Controversies exist among these listed uterine anatomic abnormalities as causes for pregnancy loss. They are suggested but not scientifically proven potential cause***s(Simpson, 2007).***

An accurate diagnosis of mullerian anomalies is essential. Imaging studies of choice include hysteroscopy, hysterosalpingography (HSG), sonohysterograms, and vaginal ultrasonography***(Homer et al., 2000).***

Surgical correction of uterine anatomic abnormalities has not been shown to benefit pregnancy outcomes in a prospective controlled trial. However, data from uncontrolled retrospective reviews have suggested that resection of the uterine septum increases delivery rates (70-85% in 1 study)***(RCOG, 2011).***