Serum Amyloid A as a Novel Marker of Morbidly Adherent Placenta

Thesis

Submitted for partial fulfillment of Master Degree

In Obstetrics and Gynecology

By

Amira El Nahas Gad El Rab Ahmed

M.B.,B.Ch. 2013 -Ain Shams University
Resident of Obstetric sand Gynecology
Ain Shams University Maternity Hospital

Under Supervision of

Prof. Hazem Amin ElZeniny

Professor of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Dr. Ahmed Sherif AbdElHamid

Lecturer in Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2017

سورة البقرة الآية: ٣٢

Acknowledgments

Firstly, thanks ***Allah*** *for giving me the strength and will to accomplish this task.*

I would like to sincerely thank **Prof. Hazem Amin ElZeniny,** *Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his encouragement and assistance to conduct this work smoothly. I really have the honor to complete this work under his supervision.*

I would also like to, wholeheartedly thank **Dr. Ahmed Sherif AbdElHamid,** *Lecturer in Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his ultimate support, meticulous supervision and guidance throughout the whole work.*

At last, my deepest and earnest indebtedness goes to my dear husband who was always in my back and without his support this work would not have ended successfully.

Amira El Nahas Gad El Rab Ahmed

List of Contents

List of Abbreviations

Abbr.	Full-term
AA	: Amyloid A
ACOG	: American College of Obstetricians and Gynecologists
ANOVA	: Analysis of variance
A-SAAs	: Acute-phase serum amyloid a proteins
CD	: Cesarean delivery
CRP	: C-reactive protein
C-SAA	: Constitutive SAA
EVT	: Extravillouscytotrophoblast cells
hCG	: Human chorionic gonadotropin
HDL	: High density lipoprotein
IHC	: Immunohistochemistry
MAP	: Morbidly adherent placenta
MMPs	: Metalloproteases
MRI	: Magnetic resonance imaging
NEC	: Normal endometrial tissues
PCR	: Polymerase chain reaction
SAA	: Serum amyloid A
SD	: Standard deviation

List of tables

List of Figures

List of Figures (Cont.)

Introduction

Morbidly adherent placenta (MAP), including placenta accreta, increta and percreta, is characterized by failure of the placenta to separate at delivery, with potential for significant perinatal and maternal morbidity and mortality ***(ACOG, 2012).***

Once rare, with an average reported occurrence of 1 in 7000deliveries during the century preceding 1972 ***(Wortman and Alexander,2013)***placenta accreta occurrence has risen steadily to 1 in 533 between the years 1982 and 2002. This ~ 13-fold increase parallels the increase in cesarean delivery (CD). When prior CD is combined with placenta previa, the risk for accreta increases with each prior CD, from 11 to 40%, 61 and67% for one, two, three and four prior CDs, respectively ***(Lyell et al.,2015).***

While multiple risk factors for MAP have been described ***(Sharp,2012)*** mechanisms of accreta development remain opaque and pre-delivery prediction is limited. Proposed mechanisms of accreta include excessivetropho blast invasion into the myometrium ***(Stanek and Drummond, 2007).***Deficient decidua enabling placental implantation onto them yometrium,

suggested by increased accreta risk with previa alone, and acombination of both ***(Wehurm et al., 2011).***

Antenatal diagnosis of accretais critical, as it can reduce maternal morbidity by enabling for a scheduled delivery by a multidisciplinary team in a tertiary care center. Ultrasound identifies many, but not all, women with MAP and without significant benefit from magnetic resonance imaging ***(D'Antonio et al., 2014).***

Serum amyloid A (SAA) is a precursor protein leading to the formation of AA fibrilsin and plays an important role in the development of systemic AA amyloidosis ***(Borbely e al., 2014).***

It is also an immunoregulatory protein involved in the acute-phasereaction. Other known functions of SAA include biological roles in lipid metabolism immunomodulation, cell proliferation, cell differentiation, cell migration, and invasion ***(Knebel et al., 2013; Sandri et al., 2014).***Each of the four isoforms of human SAA is expressed from an individual gene (*SAA1*, *SAA2*, *SAA3*, and *SAA4*). Both *SAA1* and *SAA2*encode acute-phase proteins, *SAA4* is constitutively expressed, and *SAA3* is a pseudogene. Although SAA is predominantly synthesized in the liver,5 extra-hepatic sources, including

leukocytes, adipocytes, synoviocytes, tumor cells and first trimester trophoblast cells ***(Sandri et al., 2014).***

SAA exerts immunoregulatory effects and key effects ontrophoblastic migration, invasion, and differentiation. At low concentrations, SAA regulates trophoblast invasion and metalloprotease activity within the placental microenvironment, both of which are important for placental homeostasis and placental invasion ***(Knebel et al., 2013).***

Trophoplast cells, as a key constituent of the human placenta, play a fundamental role in successful pregnancy. These cells are fated to become either villous cytotrophoblast cells, which proliferate and then differentiate via fusion to form the syncytiotrophoblast, or invasive extravillouscytotrophoblast cells (EVT), which form from proliferating cells streamingout of the syncytiotrophoblast and ultimately differentiate into amultilayered cell column ***(Gude et al., 2004)***.

These cells then proceed to detach from the column and invade the newly formed decidua, where the maternal vascular system is remodeled, establishing the maternal-fetal circulation. It is widely accepted that the invasion of EVT cells the deciduais controlled by a series of tightly regulated intercellular signaling

events mediated by growth factors, cytokines, hormones and other molecules ***(Loreger et al. 2003).***

EVT invasion is facilitated by the degradation of the endometrium/decidua extracellular matrix by various proteases, such as metalloproteases (MMPs). Insufficient migration and shallow invasion into the maternal decidua are linked to recurrent spontaneous abortion, fetal intrauterine growth restriction and pre-eclampsia ***(Bringle et al., 2010).***

Aim of the Work

This study aims to assess the changes of serum amyloid A in women with morbidly adherent placenta.

Chapter (1)
The Placenta

The placenta is literally the-tree of life. Structurally, the placenta is a hemochorial villous organ. Functionally, the placenta is a highly complex machine: (1) it acts like a lung in the exchange of oxygen and CO2; (2) it works as a digestive system, absorbing all necessary nutrients for fetal development and growth; (3) it functions as a kidney to remove wastes; and (4) it behaves as an immune barrier that protects the growing fetus from antigen attack from the maternal system***(Wang and Zhao, 2010).***

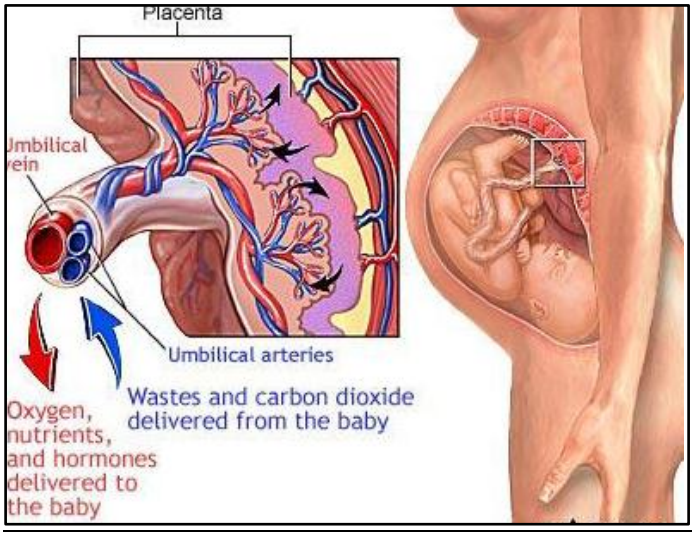

Figure (1): In the placenta, nutrients, wastes, and gases are exchanged between the mother's blood and the baby's blood (***www.aviahmidwiferyservices.com)***

The placenta is also an important endocrine organ producing many hormones and growth factors that regulate the course of pregnancy, support and promote fetal growth, and initiate parturition. However, all these tasks depend on normal vascular development within the placenta itself. Normal placental vascular development ensures a healthy pregnancy outcome, whereas insufficient or abnormal placental vascular development will compromise pregnancy outcomes both of the mother and the fetus. The functional unit of the placenta is the chorionic villus, which contains the layers of syncytiotrophoblasts/cytotrophoblasts, villous stromal, and fetal vascular endothelium that separate maternal blood from the fetal circulation ***(Wang and Zhao, 2010).***

Macroscopic appearance:

The expelled placenta is a discoid mass which weighs about 500 gm; its diameter varies from 15-20 cm, and its thickness from 3-4 cm near its center rapidly diminishing towards the periphery. Its fetal or inner surface, which is covered by the amnion is smooth and transparent, so that the mottled appearance of the chorion can be seen through it ***(Hibbard, 1989).***