UMBILICAL ARTERY DOPPLER VERSUS AMNIOTIC FLUID INDEX IN PREDICTION OF FETAL DISTRESS DURING THE THIRD TRIMESTER IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

A Thesis

Submitted for the Fulfillment of Master Degree in Obstetrics & Gynecology

Submitted by

Raghda Khaled Ahmed Hamad

(M.B.B.Ch)

Al-Gezira University

Supervised by:

Prof. Dr. Ehab Mohamed Soliman

Professor of Obstetrics & Gynecology

Faculty of Medicine -Cairo University

Prof. Dr. Mostafa Abdallah Abdelbar

Assistant Professor of Obstetrics & Gynecology

Faculty of Medicine- Cairo University

Dr. Ali Abdelhafeez Abdellatif

Lecturerof Obstetrics & Gynecology

Faculty of Medicine- Cairo University

Faculty of Medicine

Cairo University 2013

Acknowledgement

At first and foremost, thank you to ALLAH", who gave me the power to finish this work.

I find no words by which I can express my deepest gratitude to my honored ***Professor Dr. Ehab Mohamed Soliman,*** *Professor of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, for the continuous kind encouragement, support guidance and paternal advice throughout the entire work. It has been an honor and privilege to work under his generous supervision.*

Also, I would like to express my deepest thanks and appreciation to ***Professor Dr. Mostafa Abdallah Abdelbar****, Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, for his great support, and continuous advice. It has been an honor to work under his generous supervision.*

Also, I would like to express my deepest thanks and appreciation to ***Dr.Ali Abdelhafeez Abdellatif,*** *Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, for his great support, careful supervision and continuous advice which helped me to overcome numerous difficulties.*

To my family, especially my husband, for his great support, and my kids, my mother, my father, colleagues and to everyone who participated in a way or another in this work I owe my thanks and appreciation.

ABSTRACT

In pregnant women, antiphospholipid syndrome (APS) is associated with an increased risk of preeclampsia, fetal intrauterine growth restriction, and other complications related to uteroplacental insufficiency. In the last two decades, several studies were performed to identify the predictive role of some parameters in relation to obstetric outcome in APS patients. Doppler ultrasound has been used to measure the blood flow velocity in vessels during the cardiac cycle.DV flow plays a fundamental role in fetal hemodynamics. The aim of this study is to determine the role of Doppler velocimetry of the umbilical arteries, and amniotic fluid index in the prediction of fetal distress during the third trimester in patients with antiphospholipid syndrome.

Key Words:

Doppler, antiphospholipid syndrome (APS), amniotic fluid index (AFI), fetal distress.

LIST OF CONTENTS

Title	Page No.

Introduction.....1

Aim of the work.....2

REVIEW

Prediction of fetal distress.....3

Amnioticfluidindex.....29

Doppler Ultrasound.....41

Antiphospholipid Antibody Syndrome.....64

Patients and methods.....86

Results.....91

Discussion.....96

Summary.....103

Conclusion.....106

Recommendation.....107

References.....108

Arabic Summary.....

INTRODUCTION

APS is an autoimmune disorder characterized by a high-risk of obstetrical complications affecting both mother and fetus **[N. Costedoat, 2012; A. Danza, 2012]**. This condition can either be purely thrombotic, which will not be treated here, or obstetrical or it can combine both aspects of the syndrome. Clinical criteria of obstetrical APS include a history of three early miscarriages (<10 WG), and/or one intra-uterine growth restriction or a premature birth before 34 WG due to preeclampsia or eclampsia or placental insufficiency **[S. Miyakis, 2006]**. Furthermore, APS pregnant women have an increased risk of thrombosis **[J. C. Gris, 2012]**, thrombocytopenia, and HELLP syndrome **[D. Le ThiThuong, 2005].**

Preeclampsia and placental insufficiency occur in around 50% of non-treated patients and the success rate of prophylactic treatment with heparin or aspirin in respect to this is approximately 70%. Fetal death in APS is frequently preceded by intrauterine growth restriction (IUGR), oligohydramnios and abnormal heartbeats indicating hypoxia. All these symptoms may be caused by utero-placental insufficiency [Spegiorinet al. 2007].

APS can be found as a single disease and is referred as “primary.” Secondary APS is associated with other autoimmune diseases, mainly systemic lupus erymathosus (SLE). Women are more commonly affected by APS than men, in primary (3,5: 1 ratio) as well as in secondary APS (7: 1) [R. Cervera2002]. The prevalence of aPL is estimated to be 5% of the general population, and APS represents 0.5% [R. Cervera2002;R. H. W. M. Derksen2008]. However, aPL is commonly found in 15% of women with recurrent pregnancy losses (RPLs), suggesting that APS is one of the most frequent acquired etiology for RPL [R. S. Rai1995].

Repeated Doppler umbilical artery velocimetry has been reported to be an effective way tofollow pregnancies associated with APS. It provided a reliable method of studying blood flow in the utero placental circulation and strongly suggested impaired trophoblastic invasion of the placental bed, the Doppler study and AFI are important to early diagnoses of fetal distress to detect if there is:

1. Utero placental insufficiency or unacceptable exchange of oxygen and carbon dioxide by the fetus.
2. Severe placental problems caused by pregnancy-induced high blood pressure (known as pre-eclampsia or preeclampsia) and by diabetes.

Fetal distress was diagnosed when any one of the non reassuring fetal heart rate patternoccurred or when the Apgar score at birth was 6 or less.

There are several common symptoms of fetaldistress that expectant mothers and theirdoctors should watch for during pregnancy. One of the most obvious is a decrease or cessation of fetal movement. Heart rate may decrease or increase if a baby is in fetaldistress.

Aim of Work

The aim of this study is to camper the role of Doppler velocimetry of the umbilical arteries, and amniotic fluid index in the prediction of fetal distress during the third trimester in patients with antiphospholipid syndrome.

PREDICTION OF FETAL DISTRESS

Normal Fetal Growth

Human fetal growth is characterized by sequential patterns of tissue and organ growth, differentiation, and maturation that are determined by maternal provision of substrate, placental transfer of these substrates, and fetal growth potential governed by the genome **(Cunningham et al., 2005).**

The process of fetal growth comprises three consecutive and somewhat overlapping phases:

The first phase is the phase of cellular hyperplasia and encompasses the first 16 weeks of gestation.

The second phase, known as the phase of concomitant hyperplasia and hypertrophy, occurs between the 16th and 32nd weeks and involves increases in cell size and number.

The third and final phase, called the phase of cellular hypertrophy, occurs between the 32nd week and term and is characterized by a rapid increase in cell size. Quantitatively, normal singleton fetal growth increases from approximately 5g/day at 14 to 15 weeks of gestation to 10g/day at 20 weeks and 30 to 35g/day at 32 to 34 weeks, after which the growth rate decreases **(Resnik, 2002).**

In early fetal life the major determinant of growth is the fetal genome, but later in pregnancy environmental, nutritional, and hormonal influences become increasingly important **(Holmes et al., 1998).**

Fetal growth is the result of a complex interplay of various factors, which include genetic, environmental, maternal, nutritional placental & endocrine influence **(Sacks, 2004).**

The importance of identifying the determinants of fetal growth is highlighted by the fact that fetal growth restriction remains the second leading cause of perinatal

mortality, and is further enhanced by the association between low birth weight (LBW) and adult-onset disease as cardiovascular diseases and diabetes**(Barker, 1998).**

Factors that influences the fetal growth*:*

1. Maternal influences:

Various maternal factors affect fetal growth. These include maternal anthropometry, overall health, nutritional status, and genotype. Several studies have clearly demonstrated correlations between birth weight and maternal height, pre-pregnant weight, and weight gain during gestation **(Thame, 2004).**

Good maternal health is essential for proper placental implantation and normal fetal growth and development, as it allows the woman to respond and adapt appropriately to changes related to the establishment and maintenance of pregnancy. Maternal health factors limiting oxygen and nutrient delivery to the fetus have a significant negative impact on fetal growth. For instance, women with cyanotic heart disease, preeclampsia, or significant pulmonary diseases tend to have smaller infants as well as an increased risk of LBW infants. One of the most common maternal medical conditions worldwide that alters fetal growth is anemia **(Lone et al., 2004).**

2. Genetic influences:

Elements from both the maternal and the paternal genome are required for normal fetal growth and development. Recent data have demonstrated that, for certain genes, only one allele is functional. This is referred to as genetic imprinting, an epigenetic mechanism by which one of the two alleles of a gene is expressed according to its parental origin. The allele that is silenced is called imprinted that most maternally imprinted genes act as growth suppressors (e.g., H19, p57), whereas paternal ones act as growth promoters e.g., insulin-like growth factor 2, (IGF-2) **(Devriendt, 2004).**

It has been postulated that imprinting occurs because of conflicts between the maternal and paternal genome and nutrient transfer to the fetus from the mother. Thus, paternally expressed genes result in fetal growth promotion at the expense of the

mother, whereas genes that are maternally expressed would have the opposite effect **(Devriendt, 2004)**.

3. Placental influence:

The placenta influences fetal growth through its functional size, capacity to transport oxygen and nutrients, and its own metabolism. Placental growth is crucial to fetal growth. This is supported by the fact that, throughout gestation, placental growth closely parallels fetal growth. In addition, it has been demonstrated recently that placental volume measured at 14 weeks was directly related to fetal anthropometric measurements at 35 weeks **(Sacks, 2004).**

Normal and abnormal placental Development:

Normal growth of the fetus is dependent on normal placentation and growth of the placenta. The placenta is a dynamic and multifaceted organ that serves as an interface between mother and fetus with the critical role of meeting the metabolic and circulatory demands of the growing fetus.

The roles of the placenta include:

- Nutritional: Provides oxygen, glucose, amino acid, and volume (fluid) transfer.
- Immunologic: Protects the fetus from pathogens and the maternal immune system.
- Endocrinologic: Produces numerous hormones, growth factors, cytokines, and other vaso active mediators.
- Metabolic: Serves as the respiratory organ and the kidney for the fetus and is responsible for elimination of carbon dioxide, metabolic acids, and other waste products from the fetus to maintain acid base balance **(Kahn et al., 2008).**

Research has begun to provide an understanding of the complexity of the implantation and placentation processes, which require the production and coordination of numerous angiogenic growth factors (fibroblast growth factor, hepatocyte growth factor, placental growth factor, vascular endothelial growth factor),

cell-adhesion molecules, cytokines, nitric oxide, extracellular matrix metalloproteinase, hormones, and transcription factors (hypoxia-inducible factor). This process of coordination begins very early in pregnancy and can dictate whether the pregnancy grows in a normal or abnormal direction. By day 13, the cytotrophoblast layer has differentiated into invasive and noninvasive components. The invasive cytotrophoblast forms cell columns that anchor the trophoblastic tissue to the uterine epithelium and establish blood flow to the placenta and fetus. During this process, the invasive cytotrophoblast cells (extra villous trophoblast):

- Migrate through the syncytiotrophoblast and into the decidualized endometrium and myometrium.
- Invade the vessel walls of the maternal spiral arteries in these areas.
- Induce the remodeling of the spiral arteries from high-resistance to low-resistance vessels. **(Kilman, 1994)**.

As the invasive cell columns of the cytotrophoblast penetrate the syncytiotrophoblast, spaces called lacunae are created, which subsequently fuse to form the inter villous space with intervening syncytiotrophoblast columns called trabeculae. The process of inter villous space formation and spiral artery transformation directs an increasing maternal cardiac output into the inter villous space. Loss of spiral artery vessel media is the mechanism by which the spiral arteries decrease their resistance to blood flow **(Kilman, 1994).**

Angiogenesis represents the formation of new blood vessels from endothelial cells and is classified into branching and non-branching stages. **Branching angiogenesis** occurs primarily in the first and early second trimesters and leads to the formation of the immature villous tree. Branching angiogenesis continues until the mid second trimester, when there is a transition to **non-branching** angiogenesis. During this process, there is a dramatic elongation of the existing placental vascular tree. A dramatic decrease in vascular resistance and an increase in blood flow through the placenta are coincident with this process and occur via progressive loss of the musculoelastic media in the walls of the maternal spiral arterioles. The decrease in resistance is aided on the fetal side by further villous vascular branching, allowing

both fetal and maternal circulations to convert to low-resistance, high-capacitance vascular beds ***(Torry et al., 2004).***

Fetoplacental Circulation:

The **fetal circulation** is the circulatory system of a human fetus, often encompassing the entire **fetoplacental circulation** that also includes the umbilical cord and the blood vessels within the placenta that carry fetal blood.

The fetal circulation works differently from that of born humans, mainly because the lungs are not in use: the fetus obtains oxygen and nutrients from the mother through the placenta and the umbilical cord **(Whitaker, Kent 2001).**

Placental role:

The core concept behind fetal circulation is that fetal hemoglobin has a higher affinity for oxygen than does adult hemoglobin, which allows a diffusion of oxygen from the mother's circulatory system to the fetus. The circulatory system of the mother is not directly connected to that of the fetus, so the placenta functions as the respiratory center for the fetus as well as a site of filtration for plasma nutrients and wastes. Water, glucose, amino acids, vitamins, and inorganic salts freely diffuse across the placenta along with oxygen. The uterine arteries carry oxygenated blood to the placenta, and permeate the sponge-like material there. Oxygen then diffuses from the placenta to the chorionic villus, an alveolus-like structure, where it is then carried to the umbilical vein.

Circuit:

Blood from the placenta is carried to the fetus by the umbilical vein. About half of this enters the fetal *ductus venosus* and is carried to the inferior vena cava, while the other half enters the liver proper from the inferior border of the liver. The branch of the umbilical vein that supplies the right lobe of the liver first joins with the portal vein. The blood then moves to the right atrium of the heart. In the fetus, there is an opening between the right and left atrium (the *foramen oval*), and most of the blood flows through this hole directly into the left atrium from the right atrium, thus

bypassing pulmonary circulation. The continuation of this blood flow is into the left ventricle, and from there it is pumped through the aorta into the body. Some of the blood moves from the aorta through the internal iliac arteries to the umbilical arteries, and re-enters the placenta, where carbon dioxide and other waste products from the fetus are taken up and enter the maternal circulation **(Whitaker, Kent 2001).**

Some of the blood entering the right atrium does not pass directly to the left atrium through the *foramen oval*, but enters the right ventricle and is pumped into the pulmonary artery. In the fetus, there is a special connection between the pulmonary artery and the aorta, called the *ductusarteriosus*, which directs most of this blood away from the lungs (which aren't being used for respiration at this point as the fetus is suspended in amniotic fluid **(Whitaker, Kent 2001).**

Blood pressure:

It is the fetal heart and not the mother's heart that builds up the fetal blood pressure to drive its blood through the fetal circulation. Intra cardiac pressure remains identical between the right and left ventricles of the human fetus **(Johnson, P. D.J., Maxwell, 2000).**The blood pressure in the fetal aorta is approximately 30 mmHg at 20 weeks of gestation, and increases to ca 45 mmHg at 40 weeks of gestation **(Struijk, P. C. Mathews, 2008).** The fetal pulse pressure is ca 20 mmHg at 20 weeks of gestation, increasing to ca 30 mmHg at 40 weeks of gestation **(Struijk, P. C. Mathews, 2008).**

The blood pressure decreases when passing through the placenta. In the arterial umbilical it is ca 50 mmHg. It falls to 30 mmHg in the capillaries in the villi. Subsequently, the pressure is 20 mm Hg in the umbilical vein, returning to the heart **(Swiss Virtual Campus, 2011).**

Flow:

The blood flow through the umbilical cord is approximately 35mL/min at 20 weeks, and 240mL/min at 40 weeks of gestation **(Kiserud, Torvid,2004).**Adapted to the weight of the fetus, this corresponds to 115mL/min/kg at 20 weeks and 64mL/min/kg at 40 weeks **(Kiserud, Torvid,2004).** It corresponds to 17% of the

combined cardiac output of the fetus at 10 weeks, and 33% at 20 weeks of gestation **(Kiserud, Torvid, 2004).**

Endothelin and prostanoids cause vasoconstriction in placental arteries, while nitricoxide causes vasodilatation **(Kiserud, Torvid, 2004).** On the other hand, there is no neural vascular regulation, and catecholamines have only little effect **(Kiserud, Torvid, 2004).**

At birth:

At birth, when the infant breathes for the first time, there is a decrease in the resistance in the pulmonary vasculature, which causes the pressure in the left atrium to increase relative to the pressure in the right atrium. This leads to the closure of the foramen ovale , which is then referred to as the fossa ovalis. Additionally, the increase in the concentration of oxygen in the blood leads to a decrease in prostaglandins, causing closure of the ductus arteriosus. These closures prevent blood from bypassing pulmonary circulation, and therefore allow the neonate's blood to become oxygenated in the newly operational lungs **(Le, Tao; Bhushan, 2010).**

Intrauterine Hypoxia

Intrauterine hypoxia is associated with a variety of maternal, placental, and fetal conditions which may manifest differently and have different outcomes. Kingdom and Kaufmann **[J. C. P. Kingdom and P. Kaufmann 1997],** suggested to classify hypoxic pregnancy conditions into 3 subtypes: (1) pre-placental hypoxia, where both the mother and her fetus will be hypoxic (i.e., high-altitude, cyanotic maternal heart disease; etc.); (2) utero-placental hypoxia, where the maternal oxygenation is normal but the utero-placental circulation is impaired (i.e., preeclampsia, placental insufficiency, etc.); (3) post placental hypoxia, where only the fetus is hypoxic.

1. Pre-Placental Hypoxia:

Main causes of pre-placental hypoxia are a hypoxic environment (high-altitude) and pre-existing maternal cardiovascular disease such as cyanotic heart

disease, heart failure, or pulmonary hypertension. Maternal anemia, infections, and chronic inflammation may further limit the maternal oxygen uptake and oxygen delivery to the fetus, thereby increasing the risk for adverse pregnancy outcomes

Chronic hypoxia associated with placental insufficiency plays a key role in the etiology of intrauterine growth restriction (IUGR). High-altitude exposure mimics this condition and its adverse effects on birth weight exceed those of most other risk factors for IUGR, such as maternal low weight gain, smoking, prim parity, or pre-eclampsia **[G. M. Jensen and L. G. Moore 1997].** Intrauterine growth of the chronically hypoxemic fetus generally begins to slow down between gestational week 25 to 31, a time when fetal growth normally increases exponentially **[E. Krampl, C. Lees, 2000].** Interestingly, high-altitude exposure appears also to be associated with an increased risk of pre-eclampsia that may further contribute to low birth weights in high-altitude populations **[L. E. Keyes, J. F. Armaza2003].** Nevertheless, in most cases arterial hypertension during pregnancy at high-altitude is probably related to chronic hypoxia rather than to classic pre-eclampsia **[L. E. Keyes, J. F. Armaza2003– S. K. Palmer1999].** A possible explanation is that chronic hypoxia diminishes the vasodilatory effect of nitric oxide while the sympathetic nervous system (∝1-/∝2-adrenergic receptor) is activated **[M. A. Cadnapaphornchai, 2001 and S. Mateev, 2003, Zhang, D. Xiao, 2008].** In addition, potent vasoconstrictors like endothelin-1 and the hypoxia-inducible factor (HIF) are stimulated early in pregnancy by excessive generation of reactive-oxygen species (ROS) **[J. L. James, 2006].** Altitude may also influence cardiac performance and the circulating blood volume. Cardiac output is lower presumably due to a lower heart rate and smaller stroke volumes related to a decreased blood volume of women living permanently at high-altitude **[N. A. Kametas, 2004].** A direct association between uterine arterial flow and birth weight is supported by studies conducted in women from different origins,**[L. G. Moore, 2001 and C. G. Julian, 2009].**

Chronic pulmonary disease: may have similar maternal-fetal consequences as chronic exposure to hypoxia **[ACOG technical bulletin,1996].** Poorly controlled asthma is associated with pre-eclampsia, uterine hemorrhage, preterm delivery, and low birth weight **[R. Kumar,2008; E. S. Guy, A. Kirumaki, 2004].** Fetal complications include stillbirth, spontaneous preterm labor, and a need for early

delivery by Cesarean section to improve the effectiveness of maternal ventilation for respiratory failure.

Maternal hematological disorders: may directly affect oxygen transfer. Iron deficiency anemia (IDA) is common in pregnancy and often related to malnutrition or micronutrient diets **[S. Mahajan, 2008].** Sickle cell disease is particularly common in Africans and Afro-Americans **[S. C. Davies, 2000].** It may be present in combination with hemoglobin C or β-thalassemia (Hb S/C or Hb S/β). The most severe form (homozygous HbS) is called sickle cell anemia but any Hb S combination (Hb S/C or Hb S/β) can potentially cause vaso-occlusive crisis and hemolysis **["ACOG practice bulletin, 2007].** This problem is caused by the abnormal rigid sickle shape of the red blood cells with decreasing oxygen tension. Patients with sickle cell disease are at higher risk for maternal (i.e., preterm labor, preterm rupture of membranes, and postpartum infections) and fetal complications (i.e., abortion, prematurity, IUGR, low birth weight, and stillbirth) **[P. M. Sun, 2001].**

Thalassemia: is an autosomal recessive blood disease, which is particularly prevalent in Asians (α-form) and among Mediterranean people. Homozygous individuals present with severe anemia (Cooley's anemia) and extra medullary erythropoiesis.Alpha-Thalassemia major (Hb Bart's) is associated with hydrops fetalis, intrauterine death, and pre-eclampsia **[S. C. Davies, 2000].**

2. Utero-Placental Hypoxia:

Utero-placental hypoxia is related to abnormal placentation early in gestation and to placental vascular disease later in pregnancy. Abnormal placental implantation is a common finding in pregnancies complicated by IUGR, by gestational hypertension, and by pre-eclampsia. There exists an increased risk for both the mother and the fetus to develop cardiovascular disease later in life **[D. J. P. Barker,1990;J. E. Ramsay, 2003 and A. Y. Lausman,2009].**

Pre-Eclampsia: It is a complex multisystem disorder observed in human pregnancy. Maternal clinical manifestations range from mild hypertension and proteinuria to fully established HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count) **[E. J. Roccella, 2000 and B. M. Sibai, 2004].**