The proportion between the internal diameters of Yolk sac And Gestational sac at vaginal ultrasound As a predictor of The first trimesteric pregnancy outcome

A Thesis
Submitted
For partial fulfillment of Master degree in Obst. and Gyn.

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Cairo
2010

Acknowledgment

First and foremost, I feel always indebted to Allah; the kind and merciful, that this work came to light with Allah will and help.

I want to express the great honor to work under the supervision of Prof.Dr.Khaled Saiid Moussa; Professor of obstetrics and gynecology, Faculty of Medicine, Ain Shams University. He has the ability to make difficult topics easy and know the secrets of the work at a glance.

Therefore, he has given me deep guidance about the important and non-important points all through this study.

No words would be enough to describe my deepest appreciation and gratitude to Dr. Amr Mohamed El-Helaly, Lecturer of obstetrics and gynecology Faculty of Medicine, Ain Shams University for his guidance and patience through the process of this study. His sincere remarks made this work more accurate and scientific and for that, I am deeply thankful.

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Introduction

Accurate differentiation between normal pregnancy and pregnancy loss in early gestation remains a clinical challenge. Previous studies have described the association between embryonic wellbeing and characteristics of gestational sac (GS), yolk sac, amniotic cavity; embryonic heart beats ***(CHO et al, 2006).***

During organogenesis and before the placental circulation is established, the secondary yolk sac (YS) is the primary source of exchange between the embryo and the mother. The YS has nutritive, endocrine, metabolic, excretory and hemopoietic functions ***(Lindsay et al, 1992).***

The YS appears sonographically as a round and translucent structure which can be visualized as early as the 5^{th} week of pregnancy with and without the presence of a living embryo ***(Makikalli et al, 2004).***

The YS is identified in normal pregnancies by the time the mean GS diameter is 5 mm at endovaginal sonography ***(Kücük et al, 1999).***

The YS diameter and shape are sensitive predictors of pregnancy outcome ***(CHO et al, 2006; Lindsay et al, 1992; Kücük et al, 1999).*** While other studies reported that the YS measurements are not predictive of pregnancy outcome ***(Kurtz et al, 1992; Jauniaux et al, 1991).***

Another element in predicting pregnancy outcome is that GS diameter in very early pregnancy. Where there is no difference in GS diameter at 28 – 35 days from last menstrual period in normal and abnormal pregnancy. However, small than expected sac diameter in pregnancy 36-42 days from the last menstrual period is predictive of spontaneous abortion ***(OH et al, 2002).***

Demonstration of a large GS with a mean GS diameter of 16 mm or more without an embryo is an important predictor of non- viable gestation **(*Dogra et al, 2005).***

The question now is the combination of measuring YS internal diameter, GS internal diameter and getting the proportion between them, of value in predicting the first trimesteric pregnancy outcome?

Aim of the study:

To determine the value of the proportion of internal diameters of YS and GS in predicting pregnancy outcome in the first trimester.

Design: prospective study.

Patients and Methods:

Patients booked early in pregnancy for antenatal care in Ain Shams University maternity hospital. One hundred spontaneously pregnant women at 6 weeks gestation are enrolled in the study after their informed consent.

Inclusion criteria:

1- Age: from 19 – 35 years.
2- Singleton pregnancy.
3- Patient sure of her dates.

Exclusion criteria:

1- Medical diseases with pregnancy: hypertension, diabetes mellitus, heart disease.
2- Multiple pregnancy.
3- Patient is not sure of her dates.

Gestational age will be calculated according to Naegeleó s rule. Two dimensional transvaginal ultrasound will be performed with the first visit. The mean inner diameter of the YS when its image on the monitor is round and of GS is taken for each case. The patients will be followed up till the end of the first trimester to assure either miscarriage or continuation of pregnancy. Another ultrasound will be done at 13 weeks for the later cases.

Data will be analyzed statistically to know the prognostic value of YS/GS ratio in predicting the first trimesteric pregnancy outcome and its sensitivity, specificity, positive and negative predictive values.

Chapter 1
General Considerations

Many studies have focused on early gestational landmarks in an attempt to delineate normal from abnormal pregnancies. These landmarks often include the presence of an intrauterine gestational sac, yolk sac, fetal pole and heart motion ***(Deaton et al, 1997).***

The TVU has become a valuable tool in the diagnosis and management of the first trimester pregnancy ***(Dodson, 1991; Timor-Tritsch and Rottem, 1991; Deaton and Huffman, 1995).***

It is estimated that approximately 30–40% of implanted pregnancies result in spontaneous abortion during the first trimester ***(Knudsen et al 1991).*** Most of these losses usually happen very early, while the rate of spontaneous abortions after demonstration of embryonic heart activity reaches 2–5% ***(Mackenzie et al, 1988).***

While other report mentioned that 15–20% of all clinically recognized pregnancies end in spontaneous abortion ***(Dickey et al., 1992).*** It drops to less than 5% following the documentation of cardiac activity ***(Achiron et al., 1991; Nazari et al., 1991).***

So, we can conclude that about 95 % of the first trimester spontaneous abortions occur before documentation of embryonic heart motion. Since the sequence of events in early normal first trimester sonography is the appearance of GS, the YS followed by the embryonic pole and its cardiac motion. So it is logical to review the developmental anatomy, physiology and the related pathology of GS and YS.

Chorionic Sac (Gestational sac):

The early embryo in the blastocyst stage is implanted at approximately 6 to 7 days after fertilization. The embryo becomes completely embedded in the endometrial decidua at 9.5 days after conception (24 days after last menstrual period). By the end of the second week after fertilization, the conceptus has grown to a total diameter of 2 to 3 mm and can be visualized with high-frequency endovaginal transducers. During the third week after fertilization, the exocelomic cavity (The chorionic sac) —a fluid filled cavity referred to as the ‘‘gestational sac’’ by sonographers—can be seen routinely when it attains a diameter of 5 mm ***(Laing FC and Frates MC, 2000).***

Soon after the implantation of the blastocyst, the cells of the inner cell mass (embryoblast) develop into a germ disk consisting of two cell layers, (a) an endoderm germ layer that faces the cavity of the blastocyst and (b) an ectoderm layer that is attached to the trophoblast. The amniotic sac is subsequently formed between the ectoderm germ layer and the adjacent trophoblast in the 4th week of gestation by menstrual date ***(Davis, 1967; Langman J, 1975; Crowley LV, 1979).***

The cavity of the blastocyst is called the exocoelomic cavity of primitive yolk sac. As the gestational sac grows the inner lining of the primitive yolk sac shrinks or large portions are pinched off, resulting in a small secondary yolk sac, which is commonly called the “yolk sac.” The pinched off portions remain as exocoelomic cysts that are found in the extraembryonic coelom or chorionic cavity ***(Langman J, 1975).***

YS development:

Organogenesis occurs during the first 8 weeks of human embryonic development; in consequence, early human growth and development take place before and in the absence of fully developed internal organs. During this period, normal development depends on several factors, but two are imperative: nutrition and a functional transport system for the distribution of nutrients and for waste disposal ***(Pereda and Motta, 1999).***

The yolk sac (YS), a highly differentiated adnexal organ, is known to accomplish this fundamental task during early pregnancy ***(Pereda and Motta, 1999).***

In normal pregnancies, during the 3rd week of development gastrulation establishes all three germ layers in the embryo. The definitive YS communicates with the ventral aspect of the trilaminar embryo. As the embryo enlarges and lateral folding of the embryo during week 4 occurs, the base of the YS narrows and the yolk stalk forms ***(Pereda and Motta, 1999).***

The YS itself becomes more peripheral as development progresses, becoming wedged into the exocoelomic cavity but remaining connected to the midgut by the vitelline stalk. The opening between gut and YS, which is a wide space during week 4 , is transformed into a narrow lumen that extends along the slender and vascularized stalk during week 5 of embryonic development ***(O'Rahilly R, 1973).***Through the elongated yolk stalk the YS is associated temporally with the diverticulum ilei ***(Pereda and Motta, 1999).***

The new YS diameter is very constant, ranging from 4.5 to 5.0 mm. Normally, the early YS is slightly oval, while the subsequent YS appears pyriform. On its surface, the YS wall presents a network of blood vessels and is partially covered by a mucous coat. By week 11 of development, the YS becomes increasingly marginalized and the yolk stalk becomes reduced together with its narrow vitelline duct as the amniotic cavity expands. The YS degenerates at approximately the same time that its stalk becomes covered by the amnion and is incorporated into the primitive umbilical cord ***(Docherty et al, 1996).***

According to ***Sadler TW in 1990***, the connection with the midgut via the vitelline duct is also obliterated by week 11 while other report demonstrated that the vitelline duct is not functional after week 5 because of the closure of its lumen ***(Pereda and Motta, 1999).***

The YS is the most prominent structure in the gestational sac during the first 8 weeks of human embryonic development. Located outside the embryo's body during the earliest stages of human development, the YS can be easily discarded after fulfilling its temporary but vital exchange functions in early pregnancy, functions that are assumed by the placenta at a later stage ***(Docherty et al, 1996)***

Yolk sac as a major factor of success of pregnancy:

Behind every normal human embryo stands the combined contribution of the YS, the amnios, and the placenta. Nowadays there is no doubt that the YS plays a fundamental role in normal embryonic development; its absence or abnormal development implies the embryo's death ***(Nogales et al, 1993).***

Anatomy:

The secondary yolk sac (SYS) is an independent organ floating inside the fluid of the extraembryonic coelom or ECC. It forms at the beginning of the 5th week post-menstruation and develops rapidly so that by 37th menstrual day it is larger than the amniotic cavity (***Boyd and Hamilton, 1970).***

From the 6th week of gestation it appears as a spherical and cystic structure covered by numerous superficial small vessels merging at the basis of the vitelline duct. This connects the yolk sac to the ventral part of the embryo, the gut and main blood circulation. The wall of the SYS is formed by an external mesothelial layer facing the ECC, a vascular mesenchyme, and an endodermal layer facing the yolk sac cavity ***(Gonzalez-Crussi and Roth, 1976; Jauniaux et al., 1991c; Jones and Jauniaux, 1995).***
During the fourth gestational week, the primitive chorionic villi become branched and the mesenchymal cells within the villous mesoblastic core differentiate into blood capillaries, forming the primitive chorionic vascular network ***(Boyd and Hamilton, 1970; Burton, 2001).***

Around 28 days post-ovulation, the chorionic vasculature is connected to the vascular plexus of the yolk sac via the vessels of connecting stalk, and both are connected with the primitive heart via the dorsal aorta. The rich vascular network of the SYS is most certainly the first part of the fetal adnexae to be perfused when the fetal heart starts to beat. During the 10th week of gestation, the yolk sac begins to degenerate and rapidly ceases to function ***(Jauniaux et al., 1991 b).***

The yolk sac diameter measured in vivo increased significantly between 6 and 10 weeks of gestation and then decreased significantly.

Morphologically, the yolk sac showed degenerative changes after 9 weeks of gestation suggesting that the disappearance of the yolk sac in normal pregnancies was a spontaneous event of embryonic development rather than the result of mechanical compression by the expanding amniotic cavity ***(Jauniaux et al, 2005).***

The secondary yolk sac plays an important role in early human hematopoiesis and although this has not been clearly demonstrated in the human species, it could be die source of primordial germ cells ***(Hamilton et al., 1972; Moore KL, 1982; Takashina T, 1989).***

It is known that the first extrinsic hematopoietic site to appear in the embryo is located in the wall of the YS, with the emergence of hematopoietic stem cells and stromal compartments as early as week 3 of development, and that blood cells probably arise from the endodermal lining of the YS ***(Shi et al, 1985 ; Hoyes AD, 1969; Fukuda T, 1973; Takashina T, 1993 ; Ferrazzi et al, 1988 ; Moore M and Metcalf D, 1970).***

As the amnion grows and eventually fuses with the chorion, the yolk sac becomes progressively lateral and obscure, regressing to a subamniotic remnant ***(Howe R, 1996).***

Physiology of YS :

Yolk sac performs the roles of placenta, liver, bone marrow, respiratory, circulatory, renal, digestive systems and the source of stem cells of these systems ***(Pereda and Motta, 1999).***

Studies have shown that the YS has a vital function in transporting nutrients to the embryo and fulfilling exchange functions that are assumed

by the placenta, liver, and bone marrow at a later stage ***(Docherty et al 1996).***

The YS has a complex protein secretion system, ***(Gitlin D and Perricelli A , 1970; Shi et al, 1985)*** and it is also the primary source of blood that is transported to the to the embryo during a period in which the main embryogenetic processes are taking place ***(Hoyes AD , 1969; Hesseldahl H and Larsen JF, 1971; Fukuda T, 1973).***

To permit the transport of nutrients and oxygen to the embryo, a circulatory system begins at an early stage in the wall of the human YS ***(Katayama I and Kayano H, 1999)***, in addition, theYS is also considered as the source of primordial germ cells, the precursor of gametes (Witchi E, 1948), and provision of epithelia of the respiratory and digestive tracts (***Freeman et al, 1981).***

The role of the YS in nutrient supply:

The role of the YS wall in embryo nutrition and development is crucial. The functional activity of the human YS is considered to reach its peak between the 4th and 7th week of development, when the transfer of nutrients to the embryo is supposed to become very active ***(Hoyes AD, 1969).*** Survival depends on the ability of the human embryo to absorb nutrients that are produced in the YS wall and transported through the yolk stalk into the embryo's body (***Pereda and Motta, 1999).***

It is known that endodermal epithelial cells serve as the principal membrane for exchange of specific bioproducts (Hesseldahl H, Larsen JF, 1969) and are the portal for absorption of nutrients that the embryo

requires during the earliest stages of embryonic development ***(Pereda and Motta, 1999).***

Through these membrane transport activities, the YS not only provides nutrients to the embryo but probably also plays a critical role in water balance and tissue homeostasis. This involvement in absorption of substances from the vitelline cavity is deduced from the cellular features of endodermal cells ***(Hesseldahl H and Larsen JF, 1969; Pereda et al, 1994).***

The resemblance between endodermal cells and liver parenchyma has also been noted, in particular, in the presence of glycogen and microvillus-lined channels between cells that are similar to bile canaliculi and which may be important in the secretion of waste products ***(Jauniaux E and Moscoso JG, 1992; Motta PM and Porter KR, 1974; Motta PM and Fumagalli G, 1975).***

In addition, the YS synthesizes many enzymes involved in digestion and metabolism ***(Buffe et al, 1993).***

During embryonic life the YS develops as a liquid-filled organ. The YS volume increases gradually from the 5th to the end of the 10th week of gestation and then decreases ***(Jauniaux et al, 1991; Nyberg et al, 1988; Ferrazzi et al, 1988; Reece et al, 1988).***

After closure of the vitelline duct, and until the end of the embryonic period, the fluid accumulated in the lumen of the YS could also play a mechanical role, permitting the organ to keep its spherical and turgid aspect. From a functional point of view, this mechanical role is vital for normal blood cell circulation ***(Pereda and Motta, 1999).***

Yolk sac as the source of hemopoietic stem cells of the fetus:

During development, all hematopoietic tissues that are successively active during organogenesis, such as the fetal liver, thymus, spleen, and bone marrow, are colonized by extrinsic hematopoietic stem cells ***(Pereda and Motta, 1999).***

It is known that the first extrinsic hematopoietic site to appear in the embryo is located in the wall of the YS, with the emergence of hematopoietic stem cells and stromal compartments as early as week 3 of development, and that blood cells probably arise from the endodermal lining of the YS ***(Shi et al, 1985; Hoyes AD, 1969; Fukuda T, 1973; Takashina T, 1993; Ferrazzi et al, 1988; Moore M and Metcalf D, 1970).***

Other studies show that hematopoietic stem cells appear to derive from hemangioblasts that are of mesodermal origin, the final product being nucleated red cells ***(Tavassoli M, 1991).***

In consequence, the YS has been considered as the primary source of the hematopoietic stem cells that transfer stem cells from one site to the other in the whole embryonic blood system ***(Pereda and Motta, 1999).***

It is generally accepted that yolk sac-derived stem cells migrate and seed the fetal liver at approximately week 6 of development in humans ***(Moore KL and Persaud TV, 1997).***

It has been suggested that hematopoiesis is produced in the endodermal lining of the YS, before mesenchymal tissue has developed ***(Fukuda T, 1973; Bloon W and Bartelemez GW, 1940).***

From here, blood cells are either discharged into the cavity of the YS through the endodermal tubules and carried to the embryo via the vitelline duct, or are transported via blood vessels. In previous studies, blood cells within the endodermal tubule or vitelline cavity were only seen as the consequence of hemorrhage caused by mechanical damage produced during the collection of embryos; however, abundant blood cells were present intra vascularly ***(Pereda et al, 1994).***

As a whole, these observations reinforce the opinion that there still is no agreement about the site at which both vasculogenesis and hematopoiesis are initiated ***(Pereda and Motta, 1999).***

Role of YS in transport of material :

Because of the absence of maternal intervillous circulation during the embryonic period ***(Jaffe et al, 1997),*** and the need for transfer of nutrients, oxygen, and waste material to and from the embryo, the establishment of a functional vascular system is imperative for normal growth and development ***(Pereda and Motta, 1999).***

Nutrient supply is essential from early embryonic stages onward. Therefore, circulatory pathways are necessary to accomplish this early task. During human embryogenesis, with the exception of the heart, the intraembryonic circulatory system is first formed by the differentiation of endothelial cells starting at week 4 ***(O'Rahilly R and Muller F, 1987).***

However, and before these intraembryonic systems start to function, the vitelline vein carries the embryotroph from the YS into the human embryo ***(Pereda and Motta, 1999).***