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Ultrasound Evaluation of Abnormal Early Pregnancy

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Abstract: Ultrasound examination has become the "golden standard" in follow-up of the development and complications in early pregnancy. With introduction of transvaginal sonography a possibility for early morphological and biometrical ultrasound examinations has been significantly improved. The essential aim of an early pregnancy ultrasound is not only to diagnose a pregnancy, but also to differentiate between normal and abnormal pregnancy. Application of color Doppler ultrasound has enabled functional hemodynamic presentation and evaluation soon after implantation.

Key words: Early pregnancy ultrasound, morphological and biometrical ultrasound examination, differentiation between normal and abnormal pregnancy.

INTRODUCTION

The first trimester is characterized by many important landmarks with regard to the ultimate outcome of pregnancy and is mostly defined by the first 100 days of pregnancy. Woman becomes aware of her pregnancy after missing her last period and in that time she is already at least 4 weeks pregnant.[1]

A positive pregnancy test opens Pandora's box, offering more questions than answers. Although, a positive pregnancy test most likely suggests an intrauterine pregnancy. Production of human chorionic gonadotropin (hCG) occurs also by tumors (dysgerminoma, choricarcinoma) or maldevelopment of pregnancy (ectopic pregnancy or mola hydatidosa).[2] Falsely positive results are mainly obtained in the case of proteinuria, erithrocyturia or some drug intake (e.g. tranquilizers). The role of the ultrasonographer in these situations is to help the practicing clinician to evaluate pregnancy and determine the exact pregnancy status. Ultrasound evaluation of an early pregnancy includes detection of the pregnancy location (extrauterine or intrauterine), the type of pregnancy (one-fetus pregnancy, multiple pregnancy, molar pregnancy), the viability of the pregnancy and establishment of the gestational age. Evaluating pregnancy the ultrasonographer also recognizes the complications that may occur in first trimester. Ultrasound examination has become the "golden standard" in follow-up of the development and complications of early pregnancy. With introduction of transvaginal sonography (TVS) a possibility for early morphological and biometrical ultrasound examinations has been significantly improved. Application of color Doppler ultrasound has enabled functional hemodynamic presentation and evaluation soon after implantation.

Basic ultrasound markers for normal pregnancy are intrauterine gestational sac, morphologically normal embryo and its heart action.

Normal embryonic echo, in 90% of the cases suggests normal pregnancy. The possibility of early pregnancy loss is very high and can be related to fetal biometry:[3]

- CRL is < 5 mm—possibility for pregnancy loss is around 8%
- CRL measures 6 to 10 mm—possibility for pregnancy loss is around 3 to 4%
- CRL is > 10 mm—possibility for pregnancy loss is below 1%.

At present, ultrasonography is considered to be the best diagnostic method in detecting early pregnancy complications.

There is discordance between the clinicians' and embryologists' statements in determining the gestational age. Clinicians define gestational age from the first day of the last menstrual period. Embryologists do not agree with clinicians, and define the gestational age from the time of conception. Therefore, when talking about embryonic period embryologists define it as a period of organogenesis from the 3rd to the 8th week after conception, while obstetricians define it as a period from 5th to 10th week after first day of the last menstrual period.[4]

Fetal period begins after 8th week according to embryologists, i.e. after 10th week according to clinicians. As the onset of marrow formation in the humerus (the end of embryonic period according to the embryologists that occurs 56 to 57 day after ovulation[5]) is not visible by the ultrasound, for ultrasound examination and evaluation of the embryo/fetus, Blaas[6] suggests that disappearance of the physiological midgut herniation could be orientation as the end of embryonic period. The physiological midgut herniation is a macroscopically visible process, which starts after 7 completed weeks. The retraction of the bowel into the abdominal cavity occurs between approximately 10.5 to 12 completed weeks.[7] Application of 3D and 4D ultrasound seems to be advantageous in determining the points for differentiation of the embryo and the fetus.

EARLY PREGNANCY FAILURE AND VAGINAL BLEEDING

Early pregnancy failure is defined as a pregnancy that ends spontaneously before the embryo has reached by ultrasound detectable viable gestational age. The most common pathological symptom of the early pregnancy failure is the vaginal bleeding. One of the main problems in diagnosis of early pregnancy failure is why vaginal bleeding occurs. When vaginal bleeding occurs any clinician should ask several questions that can radically alter the management:

1. Is the patient pregnant?
2. Is the embryo viable or not?
3. What is the gestational age?
4. Is there any evidence to suggest that the pregnancy is ectopic?
5. If an abortion occurs, is it complete or incomplete?
6. Is there any associated pelvic mass?

Only differentiation and accurate estimation of the pregnancy status and embryo/fetus status make it possible to obtain appropriate therapeutic measures to cases where a normal outcome of the pregnancy can be expected. At this moment, ultrasonography is considered to be the best diagnostic method for detection of early pregnancy complications. For these patients the skill of the ultrasonographer is very important, since the accurate diagnosis of pregnancy failure will often result in surgical intervention.

Clinical presentation of the symptoms such as vaginal bleeding and abdominal pain, with or without the expulsion of products of conception[8] is suspected of a spontaneous abortion. For ultrasound evaluation, it is important to distinguish threatened, complete and incomplete abortion.

Threatened Abortion (Abnormal Vaginal Bleeding)

Threatened abortion is the clinical term used to describe symptom such as vaginal bleeding during the first 20 weeks of pregnancy in women who, on the basis of clinical evaluation, are considered to have a potentially living embryo/fetus. The main problem in the management of these patients is in confirming the accurate diagnosis. The threatened and spontaneous abortions together present the most common complications of early pregnancy. Sometimes, we are not even aware that a woman has been pregnant and that she aborted. If we take into the consideration these cases also, incidence of spontaneous abortions is estimated up to 70%. [9] Only 1/3 of embryos continue further development, and 50% of abortions occur before the term of expected menstruation.[9,10] These types of abortion usually cause the symptoms of sterility rather than infertility, because it seems that a woman is not even able to conceive. Thirty to forty percent of pregnancies fail after implantation, and only 10 to 15% manifest with clinical symptoms.[10,11]

In patients with a normal intrauterine pregnancy, bleeding from the chorion frondosum is undoubtedly the most common source of vaginal bleeding during the first trimester.

The development of transvaginal sonography has allowed the improved assessment of patients presenting vaginal bleeding during the first half of pregnancy, clarifying the differential diagnosis of missed abortion, ectopic pregnancy, blighted ovum and threatened abortion with a living embryo. Embryo vitality can be established reliably by documenting cardiac activity on real-time, B-mode or color Doppler ultrasonography.

Sonographic evidence of vaginal bleeding can be identified as a perigestational hemorrhage in 5 to 22% of women with symptoms of threatened abortion. However, some precautions must be taken, because the perigestational hemorrhage is occasionally difficult to distinguish from a blighted twin. The prognostic significance of identifying perigestational hemorrhage during the first trimester remains uncertain. Most of the small hemorrhages resolve without clinical sequelae, while in some cases spontaneous abortion may occur.

Incomplete and Complete Spontaneous Abortion

As a definition, **incomplete abortion** is the passage of some, but not all fetal or placental tissue through the cervical canal. In **complete abortion**, all products of conception are expelled through the cervix.[12] In incomplete abortion, the uterine debris may consist of a combination of products of conception, blood and decidua.[13]

Transvaginal ultrasonography plays important role in evaluating uterine cavity in spontaneous abortion due to detection of the retained products of conception. Retained products of conception after abortion may cause bleeding or chorioamnionitis.[14] An echogenic and vascularized mass within the uterine cavity supports the diagnosis of retained products of conception.[15] Wong and co-workers[16] reported 100% sensitivity and 80% specificity of the transvaginal sonographic examination in differentiation of the complete from incomplete spontaneous abortions. The sonographic definition incomplete

abortion is a bilayer endometrial thickness of more than 8 mm. In 29% of patients with incomplete abortion transvaginal sonography obviated the need for surgical intervention, but in 30% of patients with complete abortion detected retained products of conception. Adding color Doppler examination to basic transvaginal 2D ultrasound examination increases detection rate of the retained trophoblastic tissue.[17-19] In their recent paper, Alcázar and co-workers[20] suggested that transvaginal color Doppler is a helpful method for detecting retained trophoblastic tissue in patients with first-trimester spontaneous abortion. They analyzed 62 patients with positive urine pregnancy test and history of heavy vaginal bleeding whose gestational age was lass than 14 weeks. In each patient transvaginal ultrasound (TV US) and βHCG serum measurements were performed at the time of admission to the hospital. Retained trophoblastic tissue was suspected in the presence of low resistance floe (RI < 0.45) within the myometrium or just beneath the endometrial-myometrial interface. In 29% of women retained trophoblastic tissue was suspected and in 88.9% of these patients pathological analysis was positive for retained trophoblastic tissue. The authors suggested to perform B mode and color Doppler examination when there is suspicion on retained trophoblastic tissue (Fig. 1).

Recent studies demonstrate that risk for repeated spontaneous abortion depends exclusively on the number of previous spontaneous abortions and their cause. Even though, many different risk factors have been thoroughly researched, around 60% of unsuccessful pregnancies remain a "causa ignota".[21] The important criteria for evaluation of pregnancy loss are:[22]

- Always to keep in mind that the risk of spontaneous miscarriage is higher in older women.
- Try to uncover causes for repetitive first-trimester miscarriages. Karyotyping of couples will reveal that 3 to 8% have some abnormality, most frequently balanced chromosomal rearrangement, a translocation (other abnormalities: sex chromosome mosaicism, chromosome inversions or ring chromosomes). Besides spontaneous miscarriages, these abnormalities are associated with high-risk of malformations and mental retardation. Karyotyping is especially vital if the couple has had a malformed infant or fetus in addition to miscarriages in previous pregnancies.
- Smoking, alcohol, and heavy coffee consumption have been reported to be associated with an increased risk of recurrent pregnancy losses.[23]
- Patients with thyroid disease or uncontrolled diabetes mellitus may suffer spontaneous miscarriages although these diseases are not causes of recurrent miscarriages.
- Uterine abnormalities can result in impaired vascularization of a pregnancy, limited space for a fetus due to distortion of the uterine cavity, and incoordinate uterine contractility (See article: 2D and 3D Power Doppler Ultrasound of Endometrium as Implantation Marker).

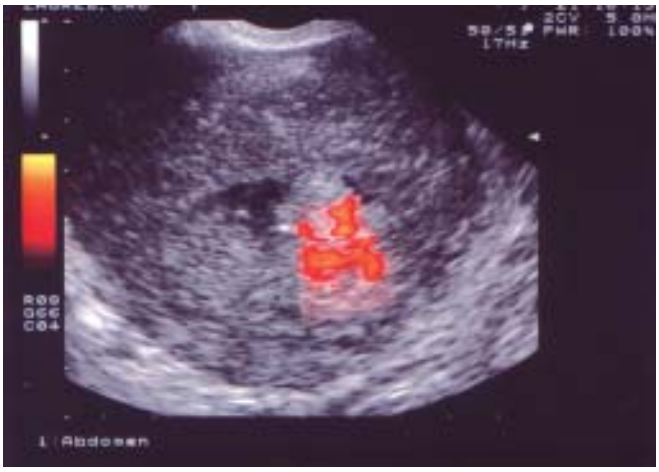

Fig. 1: Transvaginal power Doppler image of an irregular uterine cavity. Note abundant vascularity demonstrating residual placental tissue

- Looking at the first trimester miscarriage, a firm correlation with bacterial vaginosis-associated microorganisms was found in the study of Donders and colleagues.[24]
- The major cause of thrombosis in pregnancy is an inherited predisposition for clotting, especially the factor V Leiden mutation.

Immunological problems can be classified into two groups: autoimmunity (self antigens), and alloimmunity (foreign antigens). In the autoimmunity, a humoral or cellular response is directed against a specific component of the host. The lupus anticoagulant and anticardiolipin antibodies are antiphospholipid antibodies, which arise as the result of an autoimmune disease. Several series demonstrated that 10 to 16% of women with recurrent miscarriages have had antiphospholipid antibodies.[9,25] These antibodies are also associated with growth retardation and fetal death in addition to recurrent miscarriages. Preferred treatment for significant titers of antiphospholipid antibodies consists of the combination of low-dose aspirin (80 mg daily) and low-dose heparin as soon as pregnancy is diagnosed.[26,27] Unfortunately, treatment is not always successful. Alloimmunity refers to all causes of pregnancy losses related to an abnormal maternal immune response to antigens on placental or fetal tissues.

MISSED ABORTION

The diagnosis of missed abortion is determined by the ultrasound identification of an embryo/fetus without any heart activity. It is relatively easy to make this diagnosis by means of the transvaginal color Doppler ultrasound. The main parameter is the absence of the heartbeats and the lack of color flow signals at its expected position after the 6th gestational week (Fig. 2).

With the aid of sensitive color Doppler equipment it is possible to demonstrate two types of blood flow velocity waveforms from the intervillous[28] space (pulsatile arterial-like

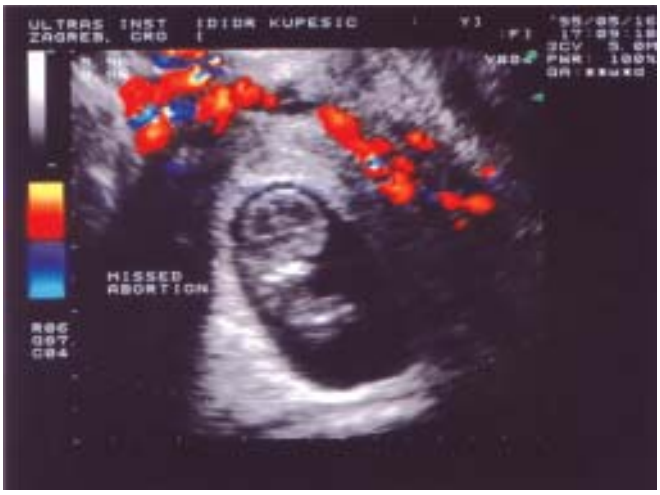

Fig. 2: Transvaginal color Doppler scan of a missed abortion. Prominent blood flow signals are obtained from the spiral arteries, while absence of heart activity is noted by color Doppler

and continuous venous like patterns) in both, normal and abnormal early pregnancies. Studies did not show any difference in terms of RI and PI of the intervillous arterial blood flow between women with missed abortion and those with normally developing pregnancy. In long-standing demise, the cessation of the embryonic portion of placental circulation leaves the fluid pumping action of the trophoblast unaffected, as it remains nourished by the maternal side of circulation. As a consequence, the embryonic circulation no longer drains a trophoblast-conveyed fluid in the villous stroma. Progressive accumulation of the fluid may result in a significant reduction of the intervillous blood flow impedance. Lower impedance to blood flow, observed in spiral arteries, indicates that a massive and continuous infiltration of the maternal blood without effective drainage causes further disruption of the maternal embryonic interface resulting in abortion. These changes can be effectively studied by 2D and 3D power Doppler.

Histological studies of the material obtained after spontaneous abortions have shown insufficient trophoblastic invasion into the spiral arteries. Such findings suggest defective transformation of spiral arteries as a possible cause of spontaneous abortion in these cases. Being aware that chromosomal abnormalities are one of the most important factors for spontaneous abortion occurring in more than 50%. It is not surprising that Doppler studies do not demonstrate any significant difference in terms of vascular resistance between normal pregnancies and those with missed abortions. Pellizzari and co.[29] pointed out that blood flow the analysis of uterine artery does not have any clinical role in the management of early pregnancies complicated by uterine bleeding.

Acharya and Morgan[30] compared 2D and 3D ultrasound findings in the first-trimester normal and abnormal pregnancies. 3D ultrasound volume measurements of intrauterine contents in normal and failed pregnancies correlated well with conventional 2D ultrasound. 3D volumetric assessment does not improve the diagnosis of abortion, but it can help in predicting pregnancies that will fail and gives possibility to determine the appropriate management regime.

BLIGHTED OVUM (ANEMBRYONIC PREGNANCY)

Blighted ovum (anembryonic pregnancy) refers to a gestational sac in which the embryo either failed to develop or died at a stage to early to visualize. The diagnosis of anembryonic pregnancy is based on the absence of embryonic echoes within the gestational sac, large enough for such structures to be visualized, independent of the clinical data or menstrual cycle. Advances in transvaginal sonography allow us to detect this kind of abnormality at a mean sac diameter of 1.5 cm.[31] If the volume of the sac is less than 2.5 ml and is not increasing in size by at least 75% over a period of 1 week, the definition of this pathological condition in early pregnancy is a blighted ovum. A large empty sac usually measures between 12 and 18 mm in mean diameter. To confirm the diagnosis, these findings should be correlated with other clinical and sonographic data including the presence of a yolk sac.

Transvaginal sonography can clearly detect existing, but a non-living embryo (embryonic demise) in some cases that undoubtedly would have been diagnosed as a blighted ovum if transabdominal sonography was the only examination performed. What the ultrasonographer would detect on his screen depends on gestational age and when the resorption process begun.

In anembryonic pregnancy, a fertilized ovum develops into a blastocyst, but the inner cell mass and resultant embryonic pole never develops. The gestational sac invades the endometrium and acts partly like a normally developing pregnancy. The syncytiotrophoblast invades the endometrium and produces human chorionic gonadotropin. Therefore, the results of a pregnancy test are positive and clinical signs of the pregnancy occur. But, the gestational sac fails to grow and develop normally, and the uterus fails to develop as expected. In this condition, the incidence of chromosomal abnormality is high. Generally, one can estimate that about 15 to 20% of all human pregnancies diagnosed before the end of the first trimester terminate in spontaneous abortion.

With falling levels of human chorionic gonadotropin, progesterone and estrogen, the feeling of being pregnant and the associated clinical signs of pregnancy that occurred earlier are lost. The diagnosis of a blighted ovum is in 100% of cases by 2D real-time ultrasonography examinations when performed a week apart after absence of embryo development has been confirmed.

Using color Doppler ultrasound in evaluation of the normal and abnormal pregnancies, Kurjak and Kupesic[32] hypothesized that lower PI from the intervillous space of the anembryonic

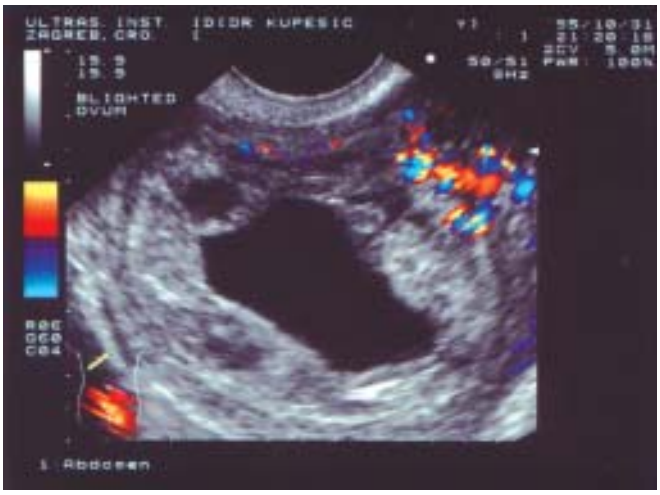

Fig. 3: Transvaginal sonogram of an anembryonic pregnancy. Note the absence of the living embryo and the yolk sac indicative of an anembryonic pregnancy. Color Doppler image presents signals obtained from the spiral arteries and other maternal vessels

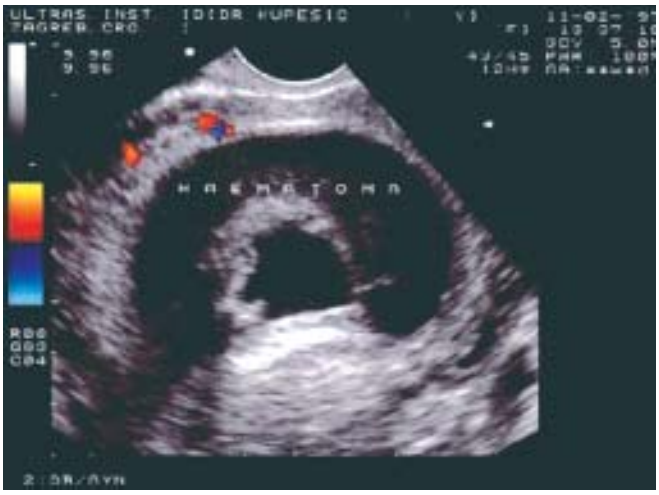

Fig. 4: Transvaginal sonogram of a large-volume hematoma located in fundal-corporeal region. Note the uterine blood flow signals on the side of the hematoma

pregnancy may reflect changes in the placental stroma, where individual villi are prone to edema. Sometimes even the embryos that measure 1 cm by transvaginal sonography may be absorbed totally after prolonged retention. Consequently, a trophoblast conveyed embryonic circulation no longer drains fluid in the villous stroma. Ongoing processes result in disruption of the maternal-embryonic interface, and finally abortion (Fig. 3).

Analyzing intervillous circulation as one of the first ultrasonographic signs of the pregnancy, studies demonstrated lower vascular resistance of the arterial-like signals in the patients with blighted ovum when compared with the normal pregnancies.

INTRAUTERINE HEMATOMAS

Intrauterine hematomas are defined as sonolucent crescent or wedge-shaped structures between chorionic tissue and uterine wall, or fetal membranes.[33] By localization we can divide them into retroplacental, subchorionic, marginal and supracervical. The most severe are large, central, retroplacental hematomas in which separation of chorionic tissue from basal deciduas occurs by mechanism similar to a mechanism of abruption of the placenta.

The most common causes of intrauterine hematoma are:

- Disturbed trophoblast invasion and defect in spiral arteries transformation
- Infection
- Mechanical factors
- Autoimmune factors
- Hematological factors

It is important to stress that finding of an intrauterine hematoma does not immediately indicate the likelihood of a spontaneous abortion. As the measure of precaution rather classify this pregnancy into a high-risk group with additional necessity for further intensive monitoring.

Prognostically, there are two main elements, which determine the pregnancy outcome. First one is the location of the hematoma. According to Kurjak and associates, location is more predictive sign than the volume of hematoma.[33,34] It is likely that if the bleeding occurs at the level of the definitive placenta (under the cord insertion), it may result in placental separation and subsequent abortion.[35] Conversely, a subchorionic hematoma detaching only a membrane opposite to the cord insertion could probably reach a significant volume before it affects normal pregnancy development.[36] Supracervical hematoma has much better prognosis because it is easily drained into the vagina and for this reason it does not represent mechanical factor for compression of the uteroplacental vessels. Higher incidence of spontaneous abortions has been reported in the cases where hematoma has been localized in the fundal or corporal region, which could be attributed to placental location in that area.[33] Retroplacental or central hematomas have the worst prognosis because they cause the largest incident of the uteroplacental circulation and placental tissue[37] (Fig. 4). The pathological mechanism is probably placental abruption, in which retroplacental clots are located between the placenta and myometrium, and pre-placental clots are found between the amniotic fluid and the placenta later in the second trimester.

Table 1 presents data on hematoma site and pregnancy outcome.[33] Kurjak and co-workers reported on increased resistance to blood flow and decrease in velocity through spiral arteries on the side of subchorionic hematoma, which is a consequence of mechanical compression of hematoma itself.[33,38] With the progression of pregnancy and growth of the trophoblastic tissue most of the hematomas gradually disappear,

Table 1: Hematoma site and pregnancy outcome

Hematoma site		*Spontaneous abortion*		*Preterm delivery*	
Site	*N*	*n*	*%*	*n*	*%*
Supracervical	30	2	6.7	2	6.7
Fundus-corpus	29	8	27.5	1	3.4
Total	**59**	**10**	**17.5**	**3**	**5**

Fisher exact test: one-tail P = 0.01, two-tail P = 0.03.
From ref.[33] with permission.

and circulation normalizes, but the pregnancy remains in the high-risk group with necessity for intensive monitoring.

Second element in diagnosis of intrauterine hematoma is its size. The modern ultrasonographic machines with transvaginal approach enable accurate evaluation of the size of the intrauterine hematoma. Intrauterine hematoma should be analyzed in relation to the trophoblast tissue, and its distance from the internal cervical os.[39] Furthermore, software of the newest machines makes possible the spatial three-dimensional image of hematomas and surrounding structures as well as measuring their volume and dynamic follow-up of biometric changes (Fig. 5). At the same time Doppler measurements can evaluate compression effect on adjacent uteroplacental circulation.[33,34]

Kupesic and co-workers[40] used color Doppler to visualize the spiral arteries in the patients affected with intrauterine hematoma. Blood flow velocity waveforms were analyzed by means of pulsed Doppler. Parameters used in the study were the resistance index (RI) and peak-systolic velocity (PVS). Table 2 presents the effect of the subchorionic hematoma on the local hemodynamics.[40]

The essential finding is that in the presence of hematomas, RI in the ipsilateral spiral arteries was increased and blood flow was decreased. Doppler measurements showed lack of the diastolic flow (RI = 1.0) in most of the patients (Fig. 6). The subchorionic hematoma compresses the spiral arteries and reduces the peak-systolic velocity. With continuation of pregnancy and reabsorption of the hematoma, impedance to blood flow returns to normal values. This statistical relationship suggests that the changes in blood flow velocity are secondary, and not the cause of subchorionic hematoma. It means that the improvement of blood flow is predictive for normal pregnancy outcome, while decreased spiral artery perfusion indicates increased risk of first- and early second-trimester loss. Since no increased risk for preterm delivery was found in patients with subchorionic hematoma, it is expected that the elevated impedance to blood flow is a transitory consequence of a compression of the arterial walls by the hemorrhage itself.

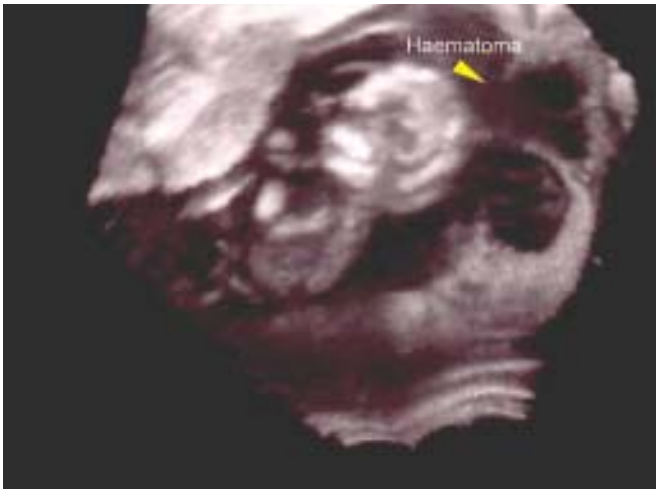

Fig. 5: Three-dimensional transvaginal sonogram of the subchorionic hematoma in a close proximity to the gestational sac

Table 2: Clinical outcome of pregnancies complicated by subchorionic hematoma. Correlation among variables

Variable	*Gestational weeks*	*Resistance index*	*Peak systolic velocity*	*Volume*
GW	1.000			
RI	–0.304	1.000		
PS	0.702	–0.791	1.000	
V	0.157	0.527	–0.276	1.000

From ref. 40 with permission.
GW—Gestational weeks; RI—Resistance index; PS—Peak systolic; V—Volume.

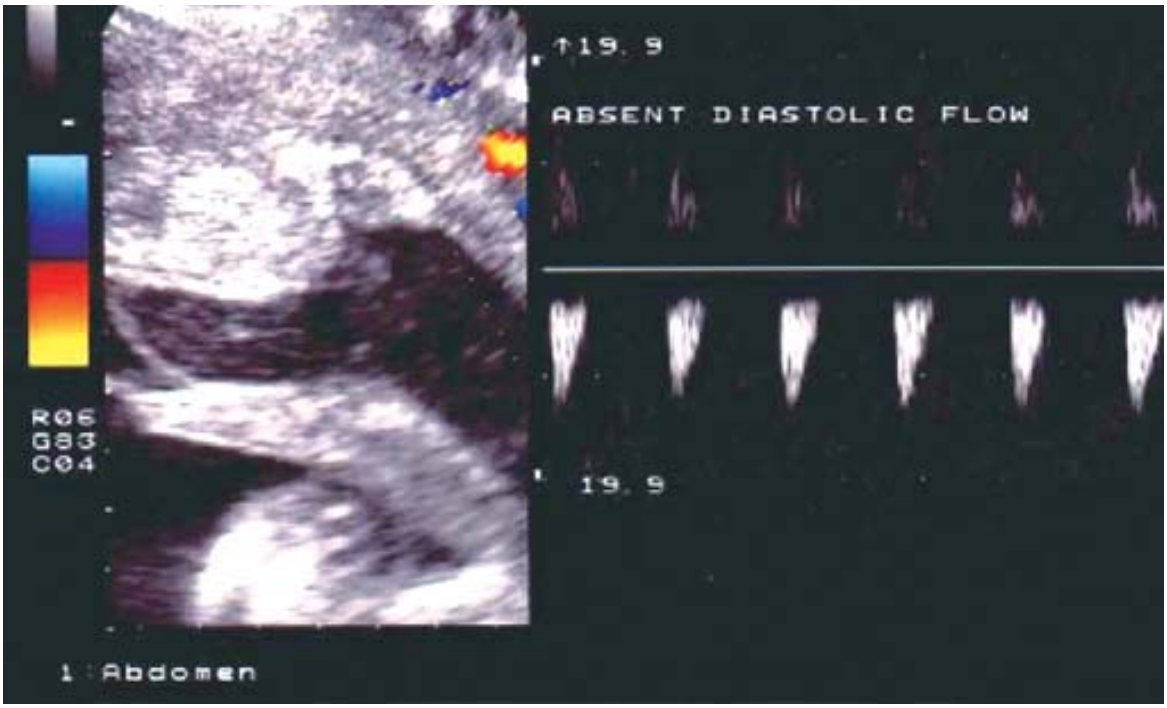

Fig. 6: Transvaginal color Doppler scan of a hematoma. Note the absence of diastolic flow (RI = 1.0) detected in spiral arteries close to the perigestational hemorrhage

ECTOPIC PREGNANCY

When the endometrium is abnormally thick or has irregular echogenicity, and intrauterine sac is not detected in the patient with the positive urinary pregnancy test, one should always think of an ectopic pregnancy.

EARLY PREGNANCY LOSS

Gestational Sac

The first visible structure within the uterus is a gestational sac. During the 5th gestational week, it measures 2 to 3 mm in diameter[41,42] as estimated by transvaginal ultrasound. The measurement should be obtained from the inner-to-inner part of the gestational sac. The gestational sac grows approximately 1 to 2 mm in size per day.[43]

Biometric and morphological characteristics of gestational sac and embryonic echo can be used as a predictive factor in diagnosis of abnormal early pregnancy. Decreased values of gestational sac diameter and/or its irregular shape can suggest upcoming incident and may be used as a marker for chromosomopathies. For example, early spontaneous abortion as one of the complications in early pregnancy usually connected with triploidy and trisomy is followed by abnormal gestational sac growth.[44,45]

By transabdominal approach abnormal gestational sac criteria include:

- Impossibility to detect double decidual sac when sac diameter is 10 mm or greater,
- Impossibility to detect yolk sac when sac diameter is 20 mm or greater, and/or
- Impossibility to detect an embryo with cardiac activity when sac diameter is 25 mm or greater.[46,47]

By transvaginal approach abnormal gestational sac criteria include:

- Impossibility to detect yolk sac when sac diameter is 8 mm or greater, or
- Impossibility to detect cardiac activity when sac diameter is 16 mm or greater.[48]

When growth rate fails to increase at least 0.7 mm/d abnormal sac and early embryo failure should be considered.[49]

Color Doppler evaluation of the supposed gestational sac is important for obtaining additional information and differentiation between the pseudogestational sac and intrauterine gestational sac. Pseudogestational sac is characterized by either absent flow around it or very low velocity flow (< 8 cm/s peak systolic velocity) and moderate resistance to blood flow (RI > 0.50).[50] Normal or abnormal intrauterine gestational sac is characterized by high velocity and low resistance pattern (RI < 0.45) (Fig. 7). As mentioned, there is

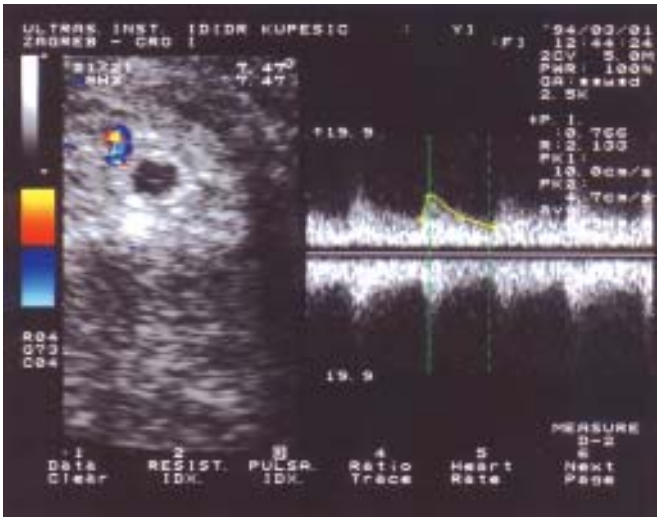

Fig. 7: Transvaginal color Doppler image of an early gestational sac. Blood flow signals derived from spiral arteries demonstrate low vascular resistance (PI = 0.77)

Fig. 8: Three-dimensional transvaginal imaging at 7-8 weeks of gestation by surface mode. Note regular shape of the yolk sac

no difference in blood flow between normal and abnormal gestational sac.[51,52]

Measurement of the gestational sac volume by 3D US can be used for the estimation of gestational age in the early pregnancy. An abnormal measurement of gestational sac could potentially be used as a prognostic marker for pregnancy outcome.[53]

Yolk Sac

Yolk sac is the first recognizable structure inside the gestational sac and should be obtained as a regularly rounded extra-amniotic structure when gestational sac reaches 8 to 10 mm.[54] Normal biometric values of yolk sac diameter during the first trimester are 3 to 6 mm (inner diameter) (Fig. 8).

Following changes assessed by 2D US are related to spontaneous abortion prediction.[54]

- Absence of the yolk sac
- Too large—more than 6 mm (over 2SD, sensitivity 16%, specificity 97%, PPV 60%),
- Too small—less than 3 mm (below 2SD, sensitivity 15%, specificity 95%, PPV 44%),
- Irregular shape—mainly wrinkled with indented walls,
- Degenerative changes—abundant calcifications with decreased translucency of the yolk sac, (Fig. 9) and
- Number of yolk sacs—has to be equal to the number of the embryos.

It is, nowadays, supposed that yolk sac abnormalities are rather the consequence than the cause of altered embryonic development.[55,56] Table 3 refers on yolk sac diameter and vascularity between 6 and 12 weeks of gestation in normal pregnancies.[55]

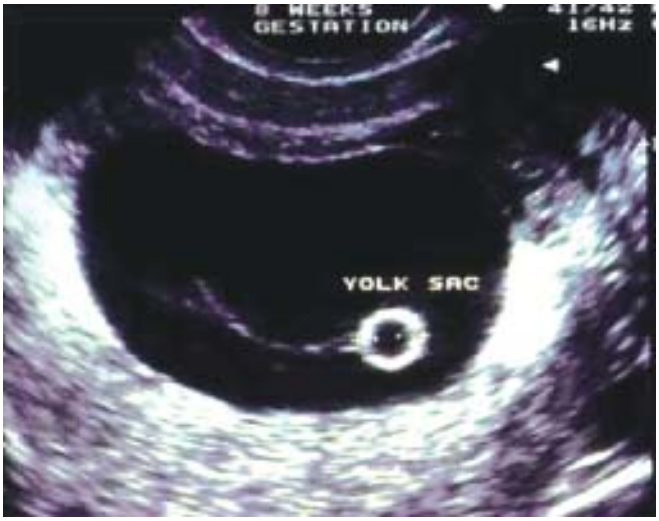

Fig. 9: Transvaginal sonogram of vitelline duct and yolk sac characterized with increased echogenicity

The ultrasound appearance of the yolk sac has already been proposed as a prognostic parameter for the outcome of pregnancy. Kurjak[33] and co-workers established sonographic criteria for distinguishing between "normal" and "abnormal" yolk sac appearance. In their experience, yolk sac should always be visible before the viable embryo; yolk sac measures 4.0 to

Table 3: Yolk sac diameter and vascularity between 6 and 10 weeks of gestation in normal pregnancies

Gestational age (weeks)	*N*	*Yolk sac diameter*			*Yolk sac vascularity*	
		Mean (range) (mm)	*Significance*	*N*	*%*	*Significance*
6	9	3.1 (2.5-3.8)		3	33.33	
7	15	3.6 (2.9-4.4)	$p < 0.05$	12	80.00	$p < 0.005$
8	19	4.1 (3.6-5.1)	$p < 0.05$	17	89.47	$p < 0.05$
9	18	4.5 (4.1-5.9)	$p < 0.05$	15	83.33	$p < 0.05$
10	14	5.3 (4.3-6.0)	$p < 0.001$	8	57.14	$p < 0.001$
11	12	5.0 (4.1-5.9)	$p < 0.05$	8	25.00	$p < 0.005$
12	10	4.3 (3.4-4.9)	$p < 0.001$	0	0	$p < 0.001$
Total	**97**	**4.2(2.5-6.0)**		**63**	**66.67**	

From ref. 55, with permission.

5.0 mm in diameter until 7 to 8 weeks of gestation and reaches 6.0 to 6.5 mm by the end of the 9th week. After that period yolk sac starts its regression and disappears at 12 weeks of gestation.[57]

The sonographic detection of abnormal yolk sac morphology may predict abnormal fetal outcome. Attempts have been made to identify abnormal parameters. Parameters of abnormal yolk sac findings listed above are predictive indicators of early pregnancy failure. All these parameters should be defined and assessed prior to 10 gestational weeks.

Abnormal yolk sac size may be the first sonographic indicator of associated failure. Primarily, the presence of an embryo without the visible yolk sac before the 10th gestational week is mostly an abnormal finding. According to some authors, the inner diameter of the yolk sac is always less than 5.6 mm in a normal pregnancy before the 10th week of gestational age. Lyons[58] established that for a mean gestational sac diameter of less than 10 mm, the yolk sac diameter should be less than 4 mm. In 15 patients who had abnormally large sacs, six had no embryo, five aborted spontaneously and only one conceptus survived. Out of nine others with embryo and large yolk sac, eight patients aborted and in one patient trisomy 21 was detected at the 24th gestational week.

The yolk sac can be too small, and this is accepted as a marker of poor pregnancy outcome. Green and Hobbins[59] analyzed a group of patients between 8 and 12 weeks' gestational age, and found out that patients with a yolk sac diameter less than 2 mm were associated with an adverse pregnancy outcome.

Most often, the shape of the yolk sac is changed when compressed by an enlarging fetus after the 10th gestational week. The normal spherical shape of the yolk sac could be distorted even earlier, requiring intensive follow-up within the next few

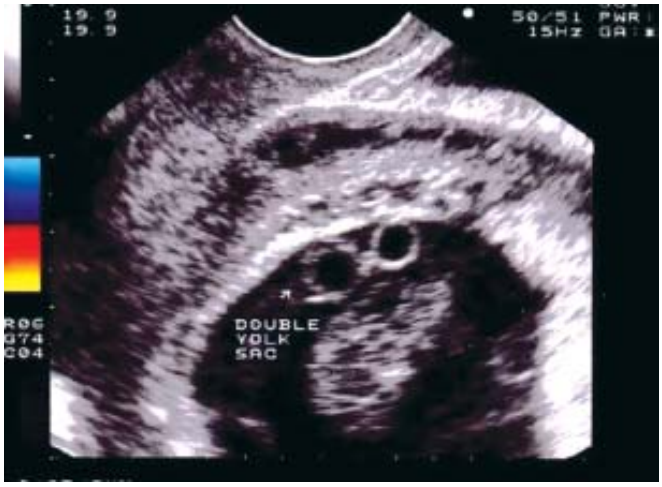

Fig. 10: Transvaginal color Doppler scan of an 8-week embryo. Note the double yolk sac close to the embryonic body

weeks. The most difficult diagnostic puzzle is the double yolk sac. (Fig. 10.) Each singleton pregnancy should have a single yolk sac. A double yolk sac is an extremely rare finding. The diagnostic puzzle includes the morphological differentiation of a retarded disappearance of physiological midgut herniation or an early abdominal wall defect.

It is unknown whether abnormalities of the yolk sac are related primarily to the yolk sac or secondary to embryonic maldevelopment. According to the present data it seems that the yolk sac plays an important role in materno-fetal transportation in early pregnancy. Changes in size and shape could indicate or reflect the significant dysfunction of this system, and therefore could influence early embryonic

development. Currently, the major benefits of the sonographic evaluation of the yolk sac are:

1. Differentiation of potentially viable and non-viable gestations,
2. Confirmation of the presence of an intrauterine pregnancy vs a decidual cast; and
3. Indication of a possible fetal abnormality.

Kurjak and associates[55] performed a transvaginal color Doppler study of yolk sac vascularization. They examined 105 patients whose gestational age ranged from 6 to 10 weeks from the last menstrual period. Transvaginal color and pulsed Doppler examination was performed before the termination of pregnancy for psychosocial reasons. The overall visualization rate for yolk sac vessels was 72.38%. A characteristic waveform profile included low velocity (5.8 ± 1.7 cm/s), and the absence of diastolic flow was found in all examined yolk sacs. The pulsatility index showed a mean value of 3.24 ± 0.94 without significant changes between the subgroups.

Kurjak and co-workers[60,61] also analyzed the vascularization of yolk sac in abnormal pregnancies. Study included 48 patients with missed abortion between 6 and 12 weeks' gestation. Yolk sac blood flow was detected in 18.54% of missed abortions. Three types of abnormal vascular signals were obtained from the yolk sac: irregular blood flow, permanent diastolic flow and venous blood flow signals. Changes in vascularization of the yolk sac noticed in missed abortions in this study are probably a consequence of embryonic death and reabsorption of the embryo through the vitelline duct. Abnormal patterns of the yolk sac vascularity can be related to decreased vitelline blood flow, which may cause progressive accumulation of nutritive secretions not utilized by the embryo. This process ends with enlargement of the yolk sac indicative of an early pregnancy failure. In 28.57% of missed abortions yolk sac vascularity was detected with large diameter of the yolk sac, and 20.00% with normal yolk sac diameter.

Yolk sac calcification was reported to result from the typical dystrophic changes that occur in nonviable cellular material.[62] Recognition of a calcified yolk sac without blood flow signals suggests long-standing demise in the first trimester, which directs the clinician for further diagnostic work-up.

Kurjak and Kupesic[61] presented data indicating that there is an interaction between the yolk sac vascularity and intervillous circulation in patients with missed abortion. In patients with long standing demise, vascular signals could not have been extracted from the hyperechoic walls of the yolk sac. Parallel assessment of the intervillous circulation demonstrated numerous color-coded areas within the intervillous space indicating low mesenchymal turgor and progressive disruption of the materno-embryonic interface. Therefore, the changes in the intervillous circulation noticed in some missed abortions are rather the consequence of embryonic death and inadequate drainage than being the primary cause of early pregnancy failure. Independent Doppler studies from three institutions using sensitive conventional and power Doppler velocimetry found that continuous and pulsatile blood flow can be extracted from intervillous space in both normal pregnancies and those with adverse outcome.[63-65]

Data presented by Kurjak and Kupesic[61] support the concept that establishment of the intervillous circulation is a progressive process during the first trimester of pregnancy. Between the 6th and 10th week of gestation clear blood flow signals are derived from the walls of the yolk sac supporting the hypothesis that yolk sac is responsible for optimal delivery of nutrients and oxygen to developing embryo up to 10 weeks of gestation. Later on intervillous circulation becomes more prominent indicating a possible switch from the vitelline towards intervillous circulation.

Three-dimensional ultrasound (3D US) significantly contributes to "*in vivo*" observation of the yolk sac surface pattern, enabling reduced scanning time and observation of the honeycomb surface pattern of the yolk sac. Automatic volume calculation allows us to estimate precise relationship between the yolk sac and gestational sac volumes, as well as to obtain the correlation between yolk sac volume and CRL measurements.[66] Distinguishing the yolk sac and embryo in 6th and 7th week of gestation decreases possibility of CRL measurement error (Fig. 11).

Table 4 reveals normal and abnormal yolk sac features.[67]

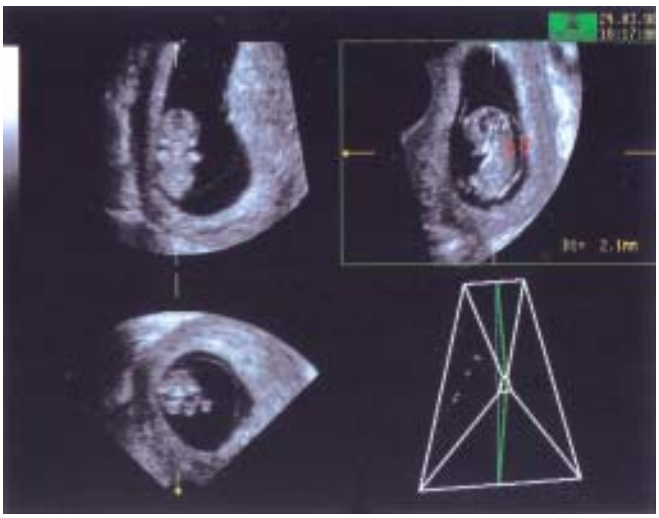

Fig. 11: Three dimensional scan of a fetus at 12 weeks gestation. Three perpendicular planes: plane A allows a frontal view of the fetal nuchal region; plane B shows an ideal mid-sagittal view of the fetus; plane C gives a symmetrical transverse section of the fetus. These planes make measurement of the nuchal translucency much easier and more accurate

Table 4: Normal and abnormal yolk sac characteristics

	Yolk sac characteristics	
	Normal yolk sac	Abnormal yolk sac
Size	5-6 mm up to 9th week of gestation	< 2 mm in 8 to 12 weeks (to small) > 6 mm after 10th week (to large)
Shape	Round	Oval, distorted
Ultrasound finding	Echoic rim, hypoechoic center	Hyperechoic
Doppler	Absence of diastolic flow	Irregular blood flow Permanent diastolic flow Venous blood flow

From ref. 67, with permission

Crown-rump Length (CRL)

Crown-rump length is used to estimate growth of the embryo and define exact gestational age. Measurement of CRL is performed in midsagittal section from the top of the head (crown) to the end of the rump of embryo by transvaginal probe.

Reliability of CRL measurements depends on embryo size and the fact that the measurements are only precise when the greatest long axis reaches 18 to 22 mm. In smaller embryos, a mistake in few millimeters means a large deviation. In embryos over 18 mm, when the real CRL is measured and the anatomic structures are visible, the possibility of a mistake is smaller.

The median CRL in fetuses with trisomies 21 and 13 or sex chromosome aneuploidies is not significantly different from the normal fetuses as reported by Kuhn and co-workers.[68] This is the reason why routine pregnancy dating should be by measurement of CRL as well as interpretation of the results from nuchal translucency or biochemical screening.

However, some results suggest that the measurement of fetal CRL may be useful predictor of spontaneous miscarriage and SGA in pregnancies with threatened abortion.[69]

Embryonic Heart Rate

The cutoff CRL for detecting cardiac activity by transvaginal probe is 4 mm,[70] and by transabdominal 9 mm.[71] Heart rate progressively increases to 120 to 160 beats /minute after 6 to 7 weeks.[72] Embryonic heart rate demonstrates certain physiologic variability within its normal range of frequencies that is 150 to 190 beats/minute for embryos bigger than 10 mm at 8 to 12 weeks of gestation. An embryonic heart rate less than 100 beats per minute (bpm) 7 weeks is recognized as embryonic bradycardia [73]. An embryonic heart rate less than 70 bpm has been reported to result in a fetal demise in 100% patients.[74] Bradycardia or arrhythmia could be considered as predictors for heart action cessation. In these cases, an early hemodynamic heart failure was noticed with consequential gestational sac enlargement, yolk sac enlargement (more than 6 mm) and initial generalized hydrops. This type of hemodynamic disturbances can occur in patients presenting with massive intrauterine hematomas prior to fetal demise.[75] Doubilet[76] reported that pregnancies in which the embryos have a slow heart rate at or before 7 weeks of gestation and which continue beyond the first trimester, have a high likelihood (90%) of congenital anomalies, compared to embryos with normal heart rates. Reduced body movements of the embryo during first and second trimester are also considered possible predictors of early pregnancy complications.[75]

Amnion Evaluation

At 6 to 8 weeks of gestation by transvaginal probe, amniotic membrane is visualized as a thin rounded structure encircling embryo. It could appear before 6th week of gestation as a linear echogenic interface projected within the gestational sac in proximity to the embryo.[42]

When the amniotic membrane is clearly visualized or its thickness and echogenicity approach that of yolk sac, it should be always suspicious to abnormal amnion development.[77] Mean amniotic sac diameter is approximately equal to the CRL in normal early pregnancy. Enlarged amniotic cavity related to the CRL suggests early pregnancy abnormality.[77]

Horrow[78] presented data on the difference between the CRL and amniotic cavity diameter and stated that in normal pregnancies it was approximately 1 mm but reached almost 9 mm in abnormal pregnancies.

In normal early pregnancy embryo is usually detected before amniotic membrane. Cases of "empty amnion" with gestational sac greater than 16 mm are highly suggestive of abnormal pregnancy and require further analysis.[79]

OBJECTS IN FIRST TRIMESTER SCREENING FOR CHROMOSOMOPATHIES

Nuchal Translucency

Increased nuchal translucency (NT) thickness at 10 to 14 weeks of gestation is associated with fetal chromosomal defects and

many genetic syndromes and abnormalities.[80,81] Measurement of NT may be obtained by transvaginal or transabdominal approach. The elements that should be kept in mind during NT measurement are:

- Embryo/fetus presented in sagittal section
- Magnification of the embryo/fetus image occupies at least 75% of the screen
- Ability to distinguish between fetal skin and amnion
- Measurement of the maximum thickness of the subcutaneous translucency, between the skin and the soft tissues overlying the cervical spine[80]
- CRL between 38 and 84 mm.

Pajkrt and co-workers[82] determined the normal range for the NT measurement in chromosomal and phenotypically normal fetuses. They demonstrated normal physiological variation in the NT thickness between 9th and 14th week of gestation. Cross-sectional data in Braithwhite's study[83] demonstrated an increase in NT measurement between 9th and 12th week, followed by the decrease at 13 and 14 weeks of gestation. Because of the change of the value of NT with CRL fixed cut of value is inappropriate and each measurement of the NT should be compared with adequate CRL value.[84] According to results of many studies NT measurement in first trimester presents one of the best ultrasonographic markers for detection of chromosomal abnormalities.[85,86]

Limitations of NT measurement by 2D US are:

- Suboptimal fetal position
- Observation of inappropriate median sagittal section of the embryo
- Attachment of the nuchal region to the amniotic membrane
- Small size of the structure to be measured [87] and
- Long lasting examination.

Performing 3D US seems to overcome some of these limitations. After storing the volume data examiner may repeat volume scanning and perform the assessment of the nuchal region from all directions.[88] (Fig. 11) Correlation of the 2D and 3D transvaginal ultrasound examinations indicated that 3D ultrasound is superior to 2D US, since using 3D US technique the midsagittal section of the fetus can be visualized with 100% success rate. Further more, the initial scan of the patient may be performed by a less experienced ultrasonographer and stored values analyzed by an expert in settled conditions. 3D US improves the accuracy of NT measurement, producing an appropriate midsagittal section of the fetus and making a clear distinction of the nuchal region from the amniotic membrane. Similarly, 3D US measurements of the NT present better intraobserver reproducibility than that conventional 2D US, increasing the effectiveness of the screening programs.[87,89]

Ductus Venosus and Heart Failure

Ductus venosus (DV), foramen ovale and ductus arteriosus Botali present specific shunts during the intrauterine life. Function of ductus venosus is connecting to umbilical circulation with inferior vena cava. DV originates from the umbilical vein and enters the inferior vein cava at the level of the hepatic veins, just below the diaphragm, forming the subdiaphragmatic venous vestibulum.[90] The main function of DV is distribution of the oxygenated blood through foramen ovale into the left atrium. In normal conditions approximately 53% of the umbilical blood flows into the DV,[91] but during the state of hypoxia rises to 70% with decrease in intrahepatic blood flow.[92] Ductus venosus blood flow signals can be depicted in the right sagittal section of the fetal abdomen as a continuation of the umbilical vein towards inferior vena cava.[93]

In normal fetuses the DV waveform shows a peak velocity during ventricular systole, another peak during ventricular diastole and a nadir during atrial contraction. The DV pulsatility index is independent of the insonation angle and proved to be the most reproducible parameter.[94] Changes in the DV waveform have been reported in different hemodynamic situations. In cardiac failure without structural defects, reversed flow during atrial contraction has been detected.[95] Similar findings have been reported in growth-restricted fetuses.[96,97] An abnormally increased DV pulsatility index may indicate a chromosomal defect.[59] Because NT is independent ultrasonographic marker, authors combined NT and DV measurement. The results from Antolín et al[98] demonstrated the usefulness of DV pulsatility index in an unselected population. Combining DV pulsatility index and NT measurement, overall sensitivity decreased to 55%, but specificity reached 99.3%, with a negative predictive value of 99.3%. When only autosomal trisomies were considered, the detection rate was similar to NT with decrease in the false positive rate. Similar effectiveness was found during the early gestational age period. These results suggest that NT may be used as a first line-screening test in order to maintain the sensitivity, while examination of the DV waveforms is useful as a second line test in order to decrease the false-positive rate, reducing the need for invasive testing to less than 1%.[99] Increased DV pulsatility index (using 95th centile) can be explained by an early cardiac failure.[100] Transient changes in DV waveform have been noted in chromosomally abnormal fetuses in early pregnancy, with a reversed flow during atrial contraction. Suggesting a temporary phenomenon Huisman and Bilardo[100] found a twin pregnancy discordant for trisomy 18 where the affected fetus at 13 weeks' gestation had an increased nuchal translucency thickness and reversed end-diastolic DV flow.[100] Transient cardiac failure has been involved in the physiology of the NT thickness. It can be hypothesized that the same early cardiac dysfunction can produce a transient fluid accumulation in the back of the neck and a temporary increase in DV pulsatility index.[101] Normal DV hemodynamics has been reported in the pathology involving the left atrium or ventricle, although blood flow from this vessel is preferentially directed

across the foramen ovale into the left heart. Abnormal DV parameters have been demonstrated in association with right ventricular pathology.[102] Malformations involving the right ventricular inlet or outlet are more commonly associated with changes in the DV waveform during atrial contraction than isolated septal defects.[94] Zoppi and all[102] found reduced absent or reversed flow in the DV during late diastole, coinciding with atrial contraction. This was considered a sign of early fetal cardiac function impairment and was observed in the first-trimester fetuses with chromosomal abnormalities that are expected to carry a more frequent rate of cardiac defects than normal. Because of the prevalence of the cardiac defects in fetuses carrying chromosomal abnormalities, it is clear that some signs of heart failure may be evident in the first trimester, and DV seems to be an essential site where this impairment could be manifested. The conclusion of this study is that DV pulsatility index should not be used as a first line screening test at 10 to 16 weeks' gestation because it does not increase the number of cases detected by NT, but can be useful as a second line test in screen-positive cases with increased NT thickness in order to increase the specificity, reducing the need for invasive testing. In chromosomally normal fetuses with an abnormal DV waveform pattern, a careful follow-up scan, including fetal echocardiography, should be mandatory.

Umbilical Artery Assessment

Analysis of the embryo/fetal umbilical artery flow shows variable results. While Zoppi and co-workers[103] demonstrated no alterations in the umbilical artery flow in embryo/fetuses with increased NT and normal karyotype and those with increased NT and trisomy 21, Borrell and co-workers[104] presented alarming data that Doppler ultrasound finding of a reversed end-diastolic flow in the umbilical artery during the first trimester of pregnancy may indicate structural and/or chromosomal defect. However, the importance of the umbilical artery flow measurements has yet to be established.

Nasal Bone

2D-ultrasound evaluation of the nasal bone in first trimester day-by-day becomes more important but also encourages academic discussion. In combination with NT, DV and biochemical markers, absence of the nasal bone indicates possibility of a chromosomal anomaly. The most common chromosomal anomaly connected with absence of the nasal bone is Down syndrome (trisomy 21). Screening regarding to this problem takes place between 11 and 14 weeks.[105] Visualization of the nasal bone should be done by transabdominal ultrasound in mid-sagittal view of the embryo/fetal profile, in an adequately magnified image, with an angle of insonation about 45 or 135° between the ultrasound beam and the line traced from the top of the chin of the embryo/fetus.[105,106]

Most recent observations suggest it is the best to visualize nasal bone in sagittal section in medial orbital angle. Cicero and coworkers in their study analyzed nasal bone at 11th to 14th week of gestation.[105]

In 99.5% of chromosomally normal fetuses nasal bone was visible. In 73% of cases with trisomy 21 nasal bone was not found. Cicero and coworkers suggests that nasal bone screening in combination with NT thickness and maternal serum biochemical analysis sensitivity could achieve 90%.[105]

Heart Analysis

Simpson and Sharland [107] analyzed association between congenital heart defects and increased NT. Their data indicate that a normal nuchal scan in no way excludes karyotype abnormalities or serious cardiac malformations. For fetuses with increased nuchal translucency, the median gestational age at time of the diagnosis of the congenital heart disease was 20 weeks. Bronshtein and Zimmer[108] suggest that transvaginal ultrasound examination of the heart in at least two main planes of four chambers and three specific images of the vessels (X, P, Y) in a period between 14th to 16th week of gestation increases possibility of detecting heart defects. Earlier diagnosis preserves entire specter of diagnostic and therapeutic options including genetic studies when indicated or therapeutic abortion. In cases of severe fetal malformations, early detection may prevent unnecessary invasive procedures.[108]

Umbilical Cord Diameter

Ghezzi and co-workers[109] analyzed NT and umbilical cord diameter in 784 patients between 10 and 14 weeks of gestation. The umbilical cord diameter was measured as outer to outer border at the maximal magnification. As the umbilical cord diameter increases with gestational age, 95th centile was cut off for enlarged diameter. The proportion of fetuses with enlarged umbilical cord diameter was higher in presence of fetal or placental chromosomal abnormalities.

Introduction of umbilical cord diameter as the ultrasonographic marker for chromosomal abnormalities slowly enters in every day practice.

COMBINED STRATEGIES FOR ANEUPLOIDY SCREENING

Unfortunately, definitive diagnosis of the aneuploidy still can only be accomplished by invasive procedures. Certain ultrasonographic markers such as (abnormal NT, DV and nasal bone) refer to possibility of existence of chromosomal abnormality. Trying to create an efficient non-invasive screening test clinicians combined ultrasonographic and non-ultrasonographic markers. Sabria and co-workers[110] presented data from their 13 years long experience in prenatal screening with detection rate of 90.0% at 5.5% false-positive rate for trisomy 21, detection rate of 75.0% at 1.0% false-positive rate

for trisomy 18 and detection rate of 87.5% at 5.2% false-positive rate for all-aneuploidies. Their suggestion for first trimester ultrasound screening is to combine:

- Maternal age
- NT as ultrasound marker, and
- PAPP-A and free ßHCG as biochemical markers.

This combination detects between 85 and 90% of Down's syndrome, at the 5% false positive rate.[111-113] Similar results are presented in retrospective studies for trisomy 13 and Turner's syndrome, while sex trisomies are usually not detectable.[114,115]

Introducing nasal bone as the independent ultrasonographic marker and using color Doppler evaluation of DV, as a second line marker Sabria suggests that detection rate for trisomy 21 will be 98 % at 5% false-positive rate.

Comas and co-workers[116] suggested for low-risk population single NT measurement or selective screening by NT and DV assessment, and for the high risk population combined simultaneous screening (including all sonographic, Doppler and biochemical parameters), all in sense of reducing invasive testing procedures.

CONCLUSION

Ultrasound examination has become the "golden standard " in follow-up of the development and complications in early pregnancy. With introduction of transvaginal sonography a possibility for early morphological and biometrical ultrasound examinations has been significantly improved. The essential aim of an early pregnancy ultrasound is not only to diagnose a pregnancy, but also to differentiate between normal and abnormal pregnancy. Application of color Doppler ultrasound has enabled functional hemodynamic presentation and evaluation soon after implantation.

Early pregnancy failure is defined as a pregnancy that ends spontaneously before the embryo has reached by ultrasound detectable viable gestational age. The most common pathological symptom of the early pregnancy failure is the vaginal bleeding. Only differentiation and accurate estimation of the pregnancy status and embryo/fetus make it possible to obtain therapeutic measures to cases where a normal outcome of the pregnancy can be expected.

The development of transvaginal sonography has allowed improved assessment of the patients presenting vaginal bleeding during the first half of pregnancy, clarifying the differential diagnosis of missed abortion, ectopic pregnancy, blighted ovum and threatened abortion with a living embryo. Embryo vitality can be established reliably by documenting cardiac activity on real-time, B-mode and/or color Doppler ultrasonography.

Threatened abortion is the clinical term used to describe vaginal bleeding during the first 20 weeks of pregnancy in women who, on the basis of clinical evaluation are considered to have a potentially living embryo/fetus. With a normal intrauterine pregnancy, bleeding from the chorion frondosum is undoubtedly the most common source of vaginal bleeding during the first trimester and should be considered in the diagnosis of threatened abortion.

As a definition, incomplete abortion is the passage of some, but not all fetal or placental tissue through the cervical canal. In complete abortion, all products of conception are expelled through the cervix. Transvaginal ultrasonography plays an important role in evaluating uterine cavity in spontaneous abortion since it enables detection of the retained products of conception. Retained products of conception after abortion may cause bleeding or endometritis. Recent studies demonstrate that the risk for repeated spontaneous abortion depends exclusively on the number of previous spontaneous abortions, their cause, maternal age, chromosomal abnormalities, uterine anomalies etc. Even though, many different risk factor have been thoroughly researched around 60% of unsuccessful pregnancies remain unknown.

In patients with a suspicion on a spontaneous abortion it is suggested to perform not only 2D but also color Doppler sonographic evaluation of the retained trophoblastic tissue.

The diagnosis of missed abortion is determined by the ultrasound identification of an embryo/fetus without any heart activity. It is relatively easy to make this diagnosis by means of the transvaginal color Doppler ultrasound. The main parameter is the absence of the heartbeats and the lack of a color flow signals at its expected position after the 6th gestational week.

Blighted ovum (anembryonic pregnancy) refers to a gestational sac in which the embryo either failed to develop or died at a stage to early to visualize. The diagnosis of anembryonic pregnancy is based on the absence of embryonic echoes within the gestational sac large enough for such structures to be visualized independent of the clinical data or menstrual cycle. Advances in transvaginal sonography allow us to detect this kind of abnormality at a mean sac diameter of 1.5 cm. To confirm the diagnosis, these findings should be correlated with other clinical and sonographic data including the presence of a yolk sac.

Intrauterine hematomas are defined as sonolucent crescent or wedge-shaped structure between chorionic tissue and uterine wall, or fetal membranes. By localization intrauterine hematomas can be divided into retroplacental, subchorionic, marginal and supracervical. The most severe are large, central, retroplacental hematomas. Prognostically, there are two main elements which determine the pregnancy outcome: location and the size of the hematoma. The essential color Doppler finding is that in the presence of hematomas, vascular resistance in the ipsilateral spiral arteries is increased and blood flow is decreased. Doppler measurements showed lack of the diastolic flow in most of hematomas resulting in RI of 1.0. Since no increased risk for preterm delivery was found in patients with subchorionic hematoma, it is expected that the elevated impedance to blood flow is a transitory consequence of a compression of the spiral arterial walls by the hemorrhage itself.

Biometric and morphological characteristics of gestational sac and embryonic echo can be used as predictive factors in diagnosis of abnormal early pregnancy. Decreased values of gestational sac diameter and/or its irregular shape can suggest upcoming incident and could be used as markers for chromosomopathies. When growth rate fails to increase at least 0.7 mm/d an early embryo failure should be considered.

Yolk sac is the first recognizable structure inside the gestational sac in early pregnancy. Following changes assessed by 2D US are related to the prediction of the spontaneous abortion: absence of yolk sac, too large yolk sac (more than 6 mm), too small yolk sac (less than 3 mm), irregular shape of the yolk sac (mainly wrinkled with indented walls), degenerative changes of the yolk sac (abundant calcifications with decreased translucency of yolk sac), and number of yolk sacs (has to be equal to the number of the embryos).

Crown-rump length (CRL) is used to estimate growth of the embryo and define exact gestational age. The median CRL in fetuses with trisomies 21 and 13 or sex chromosome aneuploidies is not significantly different from that of the normal fetuses. An embryonic heart rate less than 100 beats per minute (bpm) before 7 weeks is recognized as embryonic bradycardia. Bradycardia or arrhythmia could be considered as predictors for heart action cessation. In these cases, an early hemodynamic heart failure is usually noticed with consequential gestational sac enlargement, yolk sac enlargement (more than 6 mm) and initial generalized hydrops.

Mean amniotic sac diameter is approximately equal to the CRL in normal early pregnancy. Enlarged amniotic cavity related to the CRL suggests early pregnancy abnormality.

Increased NT thickness at 10 to 14 weeks of gestation is associated with fetal chromosomal defects, many genetic syndromes and abnormalities. Because of the change of the value of NT with CRL, each measurement of the NT should be compared with adequate CRL value. First trimester ultrasound screening should include: maternal age, NT as ultrasound marker and PAPP-A and free ßHCG as biochemical markers. These parameters have detection rate of 90.0% at 5.5% false-positive rate for trisomy 21, detection rate of 75.0% at 1.0% false-positive rate for trisomy 18 and detection rate of 87.5% at 5.2% false-positive rate for all-aneuploidies.

In normal fetuses the DV waveform shows a peak velocity during ventricular systole, another peak during ventricular diastole and a nadir during atrial contraction. Results of different studies suggest that NT should be used as a first line-screening test in order to maintain the sensitivity, while examination of the DV waveforms can be useful as a second line test in order to decrease the false-positive rate, reducing the need for invasive testing to less than 1%.

In combination with NT, DV and biochemical markers absence of the nasal bone indicates possibility of a chromosomal anomaly. Introducing nasal bone as the independent additional ultrasonographic marker and using color Doppler evaluation of DV, as a second line markers it is suspected that detection rate will be 98 % at 5% false-positive rate for trisomy 21.

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