TRANSVAGINAL EVALUATION OF THE 1ST TRIMESTER: NORMAL AND ABNORMAL

IMPLANTATION

An adequate endometrial thickness (? 8 mm)[1], as well as appropriate vascularization are required for implantation. The uterine glands provide early embryonic nutrition through the placenta intervillous space (Fig. 1)[2].

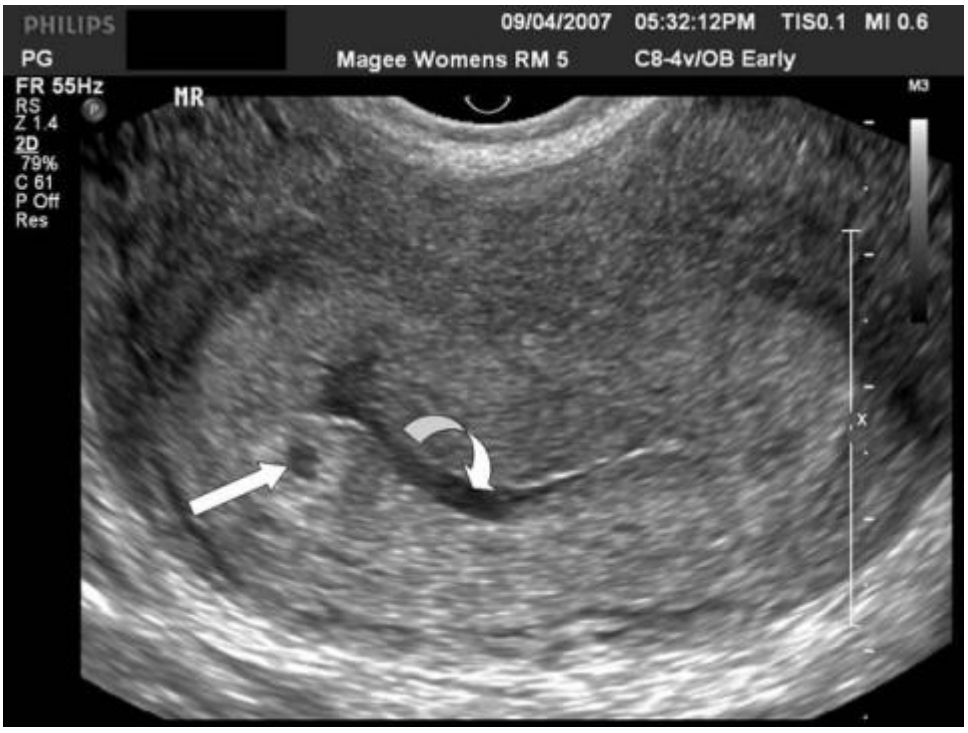

Figure 1 - Posterior implantation of a 4 week gestational sac (arrow). Fluid is present within the endometrial cavity (curved arrow).

Implantation most commonly occurs on the posterior uterine wall approximately 0.5 cm to 1.5 cm from the fundus (Fig. 2)[3]. Kawakami et al[4] reported that 17 of 21 gestational sacs were located on the ipsilateral uterine wall to the ovulating ovary. There is a decrease in uterine artery impedance prior to implantation. A delay in this process[5] and/or poor endometrial blood flow may result in miscarriage[2].

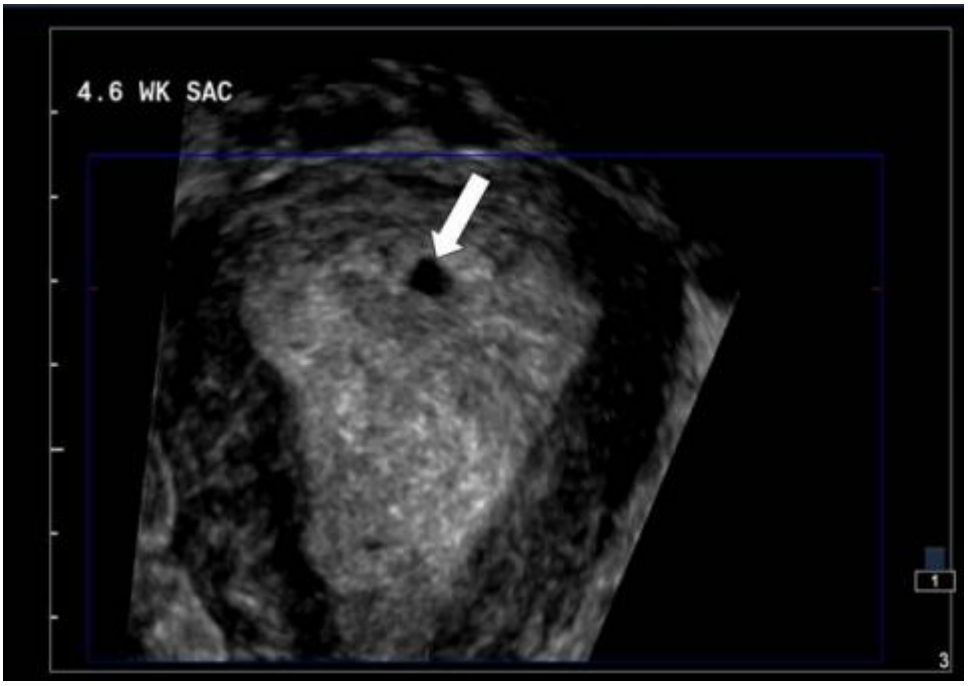

Figure 2 - 3D coronal image of the endometrial cavity. A gestational sac (4.6 menstrual weeks) is appropriately implanted in the posterior endometrium.

GESTATIONAL SAC

The 1st trimester gestational sac is structurally and functionally distinct. The embryo develops in an environment that is lower in oxygen then that of the fetus.

Part of the cytotrophoblast differentiates into extravillous trophoblast that invades the spiral arteries and adapts these vessels to provide the increased blood flow required in the 2nd and 3rd trimesters. However, as they invade the vessels in the early 1st trimester, they form plugs to occlude the spiral arteries and prevent maternal blood from entering the intervillous space[6].

Antioxidant enzymes are not expressed by the syncytiotrophoblast until 8 to 9 weeks' menstrual age. Hence, the early trophoblast is extremely sensitive to oxygen mediated damage. As these enzymes develop, the trophoblast plugs loosen and the placenta is exposed to increasing oxygen concentrations[6]. In two-thirds of early pregnancy failures, there is defective placentation with reduced cytotrophoblast invasion and impaired formation of the trophoblastic plugs. The premature onset of the maternal circulation to the villi increases oxygen concentration and thereby impairs syncytiotrophoblast function. This results in a fall in hCG and subsequent miscarriage[7].

Significant intervillous flow is not well established until 10 weeks' menstrual age[8]. The intraplacental oxygen concentration increases from < 20 mm of mercury at 10 weeks' menstrual age to > 50 mm of mercury at 12 weeks' due to the onset of the intervillous circulation[9]. Early Doppler studies[10] could not detect intervillous blood flow until after 12 weeks' menstrual age. Burton et al[8], therefore, suggested that one of the functions of trophoblastic plugging of the spiral arteries was to restrict maternal blood flow into the intervillous space. With more sensitive Doppler equipment intervillous flow has been detected throughout the 1st trimester with a significant increase after 11 weeks' menstrual age[11]. The dissipation of the intervillous plugs begins at the periphery of the placenta at 8 weeks' menstrual age[12]. Hence, the development of the intervillous circulation seems to increase progressively throughout the 1st trimester[13]. In patients with a threatened miscarriage, a subchorionic hemorrhage results from bleeding in this peripheral area. However, with an embryonic demise, bleeding may occur centrally or throughout

the placenta[7].

The early gestational sac refers to the chorionic cavity. The gestational sac may be visualized with transvaginal sonography as early as 4 to 4.5 weeks' menstrual age[14]. A gestational of 5 mm is consistent with 5 weeks' menstrual age. The echogenic rim around the gestational sac (? 2 mm) is due to the surrounding chorionic villi and decidual reaction[15].

The fluid in the amniotic cavity is anechoic. The proteinaceous material in the chorionic cavity produces low-level echoes (Fig. 3)[16]. Protein electrophoresis indicates that the chorionic fluid is an ultra-filtrate of maternal serum. The presence of a higher concentration of hCG in the chorionic cavity than in maternal serum indicates that there is a direct pathway between the trophoblast and chorionic cavity. Hence, the chorionic cavity provides a nutritional pathway to the embryo prior to the development of the uteroplacental circulation[7]. Maternal hyperglycemia impairs the function and structure of the yolk sac and is believed to be associated with diabetes related malformations[17]. Human chorionic gonadotropin [hCG] levels indicate the health of trophoblastic tissue. In some cases of anembryonic pregnancies the Beta hCG level may be normal for the patient's true gestational age and sonographically the trophoblastic reaction (echogenic rim) has a normal appearance and thickness. Low levels of Beta hCG are associated with a poor decidual reaction and a thin echogenic lining of < 2 mm15,[18].

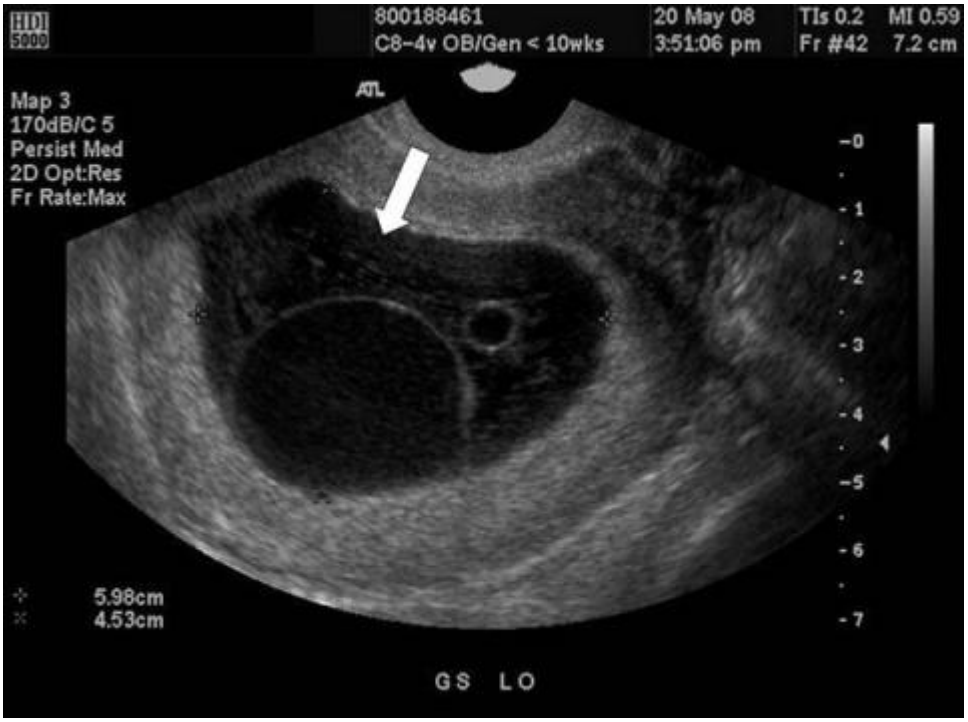

Figure 3 - 8.4 week gestational sac. The proteinaceous material in the chorionic cavity (arrow) is apparent.

DISCRIMINATORY ZONE

HCG that is produced by trophoblastic tissue is detectable 8 days after conception[19]. The concept of a discriminatory bhCG zone at which a gestational sac should be visualized with ultrasound was introduced by Kadar et al[20]. A range of 1,000-2,000 mIU/ml is widely accepted for transvaginal sonography[21]. However, biologic variability in singleton gestations and the possibility of twins must be considered. Nearly all intrauterine gestational sacs should be identified by an bhCG of 3,000 mIU/ml[22]. A yolk sac is identified by a bhCG of 5,000 mIU/ml and embryonic cardiac activity is visualized by a bhCG of 15,000 mIU/ml[14].

CHORIONIC CAVITY

The chorionic fluid volume approximately doubles between 6 and 8 weeks' menstrual age. The maximum chorionic cavity fluid volume of 6 ml occurs at approximately 9 weeks' menstrual age[23]. By 10 weeks' gestation embryonic renal function is initiated, resulting in a rapid expansion of the amniotic cavity. By the end of the 2nd trimester the amnion and chorion have fused.

The mean gestational sac diameter is determined by averaging three perpendicular diameters (Fig. 4). Between 5 and 6 menstrual weeks, the gestational sac normally increases in size by 1 mm/day in mean diameter[7]. Prior to visualization of the embryo, menstrual age (days) can be calculated by adding 30 to the mean sac diameter[19]. The mean gestational sac diameter has a reported variability that ranges from ± 7 to ± 12 days[24]. Hence, once a crown-rump length is visualized, its increased accuracy indicates that it should be used for gestational age assessment.

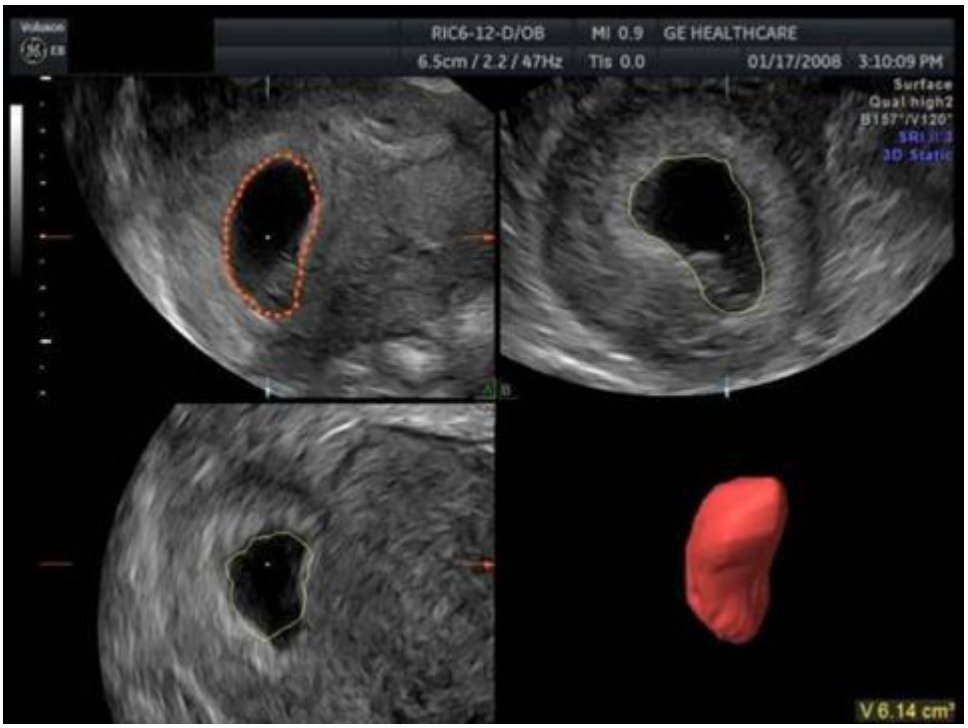

Figure 4 - Three-dimensional volume of gestational sac.

Prior to 9 weeks' menstrual age, a small gestational sac (Fig. 5), i.e. small chorionic cavity, is one factor that has been associated with a higher miscarriage rate. Bromley et al[25] followed 16 pregnant women with a mean sac diameter minus crown-rump length < 5 mm and reported a miscarriage rate of 94% (15 of 16 cases). In one retrospective study, a small gestational sac was present before embryonic demise in 10.7% of cases[26]. The predictive value of small gestational sac is also dependent upon the clinical history (i.e. maternal age, presence or absence of vaginal bleeding, etc).

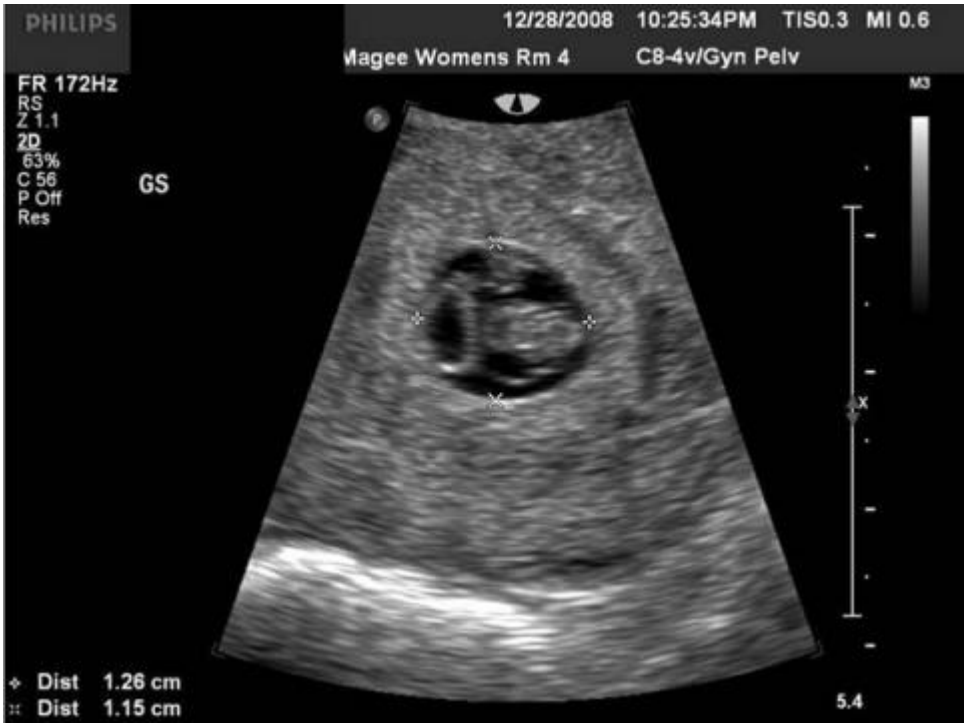

Figure 5 - Small gestational sac: 5.4 week gestational sac; 7.0 week crown-rump length.

Although the gestational sac dimensions correlate with gestational age, a cut-off to accurately differentiate between normal pregnancies and miscarriages has not been established. Rempen et al[27] suggested an empty gestational sac cut-off of > 18 mm was diagnostic of a non-viable pregnancy. However, Elson et al[28] were able to document two viable pregnancies with an empty sac > 18 mm. Luise et al[29] subsequently defined an anembryonic pregnancy as a gestational sac > 20 mm without a yolk sac. Hence, whenever there is uncertainty about a patient's gestational age parameters and/or viability on an ultrasound exam, a repeat scan at an interval of one week should be obtained before a definitive diagnosis is made.

Traditionally, embryonic resorption (i.e. prior sonographic documentation of an embryo with cardiac activity that is no longer detectable) has not been considered the same as an anembryonic pregnancy. However, anembryonic pregnancies have been found to contain alpha-fetoprotein of yolk sac origin. The latter finding indicates that an embryo developed until at least 14 days after ovulation when a secondary yolk sac would be present. Most anembryonic pregnancies are, therefore, pregnancies in which the embryo has been absorbed rather than never present[30].

AMNIOTIC CAVITY

Between 6.5 and approximately 10 weeks' menstrual age the diameter of the amniotic cavity is approximately 10% greater than the crown-rump length (Fig. 6)[27]. Hence, there is a linear correlation between amniotic cavity volume and gestational age. Once the amniotic cavity is easily detectable with transvaginal sonography, an embryo should also be identified. A disproportionately enlarged amniotic cavity in the first half of the 1st trimester is associated with an early embryonic demise (Fig. 7)[31]. An empty amnion is also associated with early pregnancy failure[32].

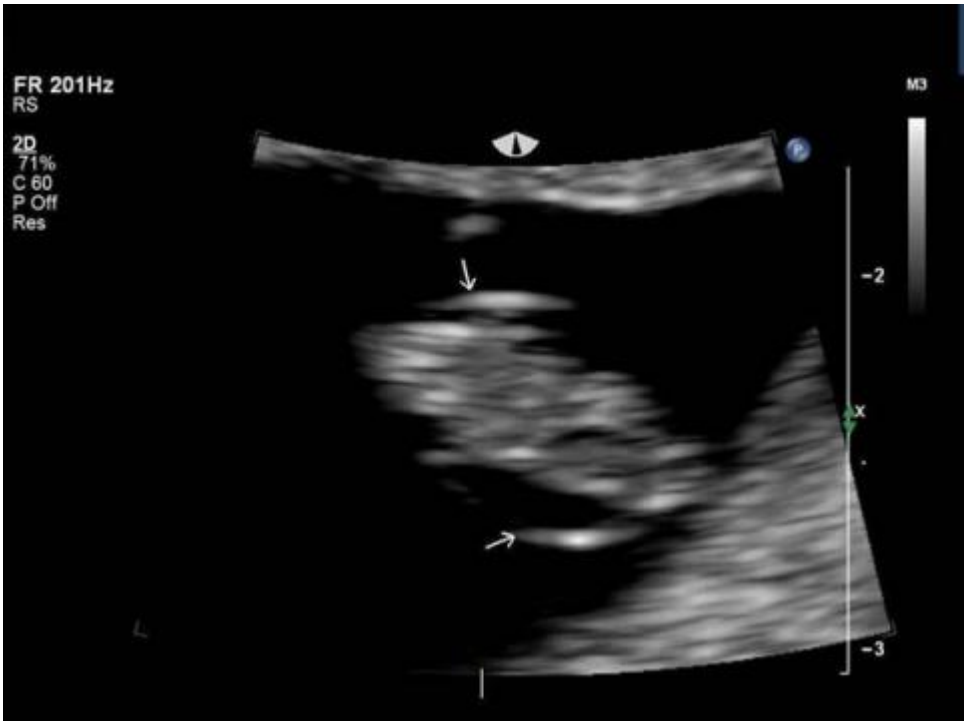

Figure 6 - Amniotic cavity (arrows) at 7 weeks' menstrual age.

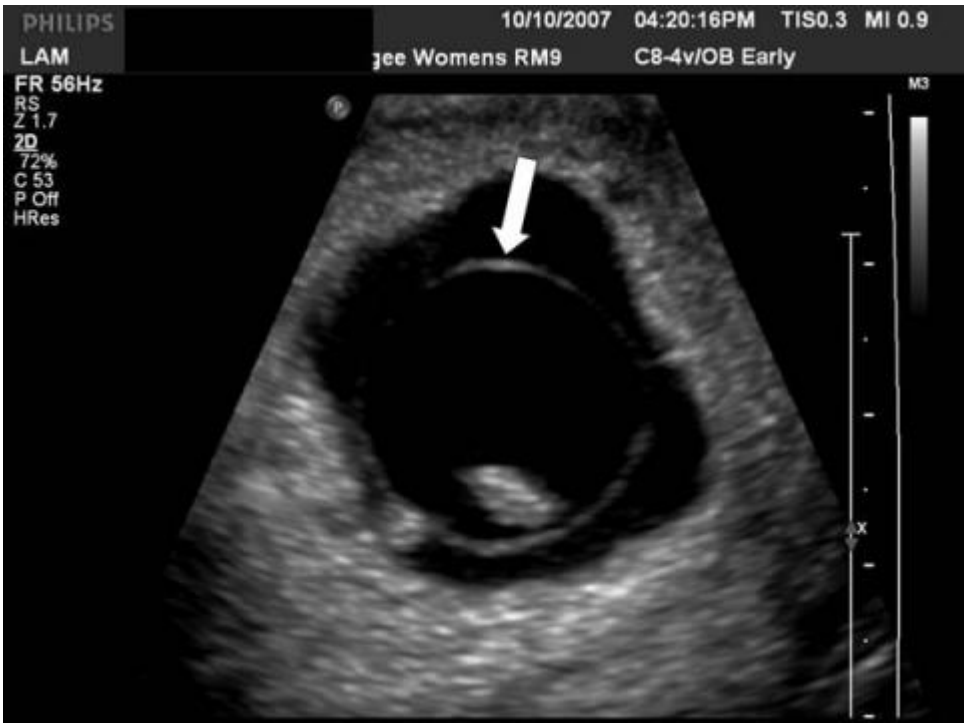

Figure 7 - Embryonic demise with an enlarged amniotic cavity (arrow).

YOLK SAC

The yolk sac (Fig. 8) plays a critical role in embryogenesis. The functions of the yolk sac include:

1. Provision of nutrients to the embryo before a placental circulation is established
2. Embryonic hematopoiesis
3. Origin of the epithelial lining of the gastro-intestinal and respiratory tracts
4. Production of albumin, alphafetoprotein and other proteins during the embryonic period

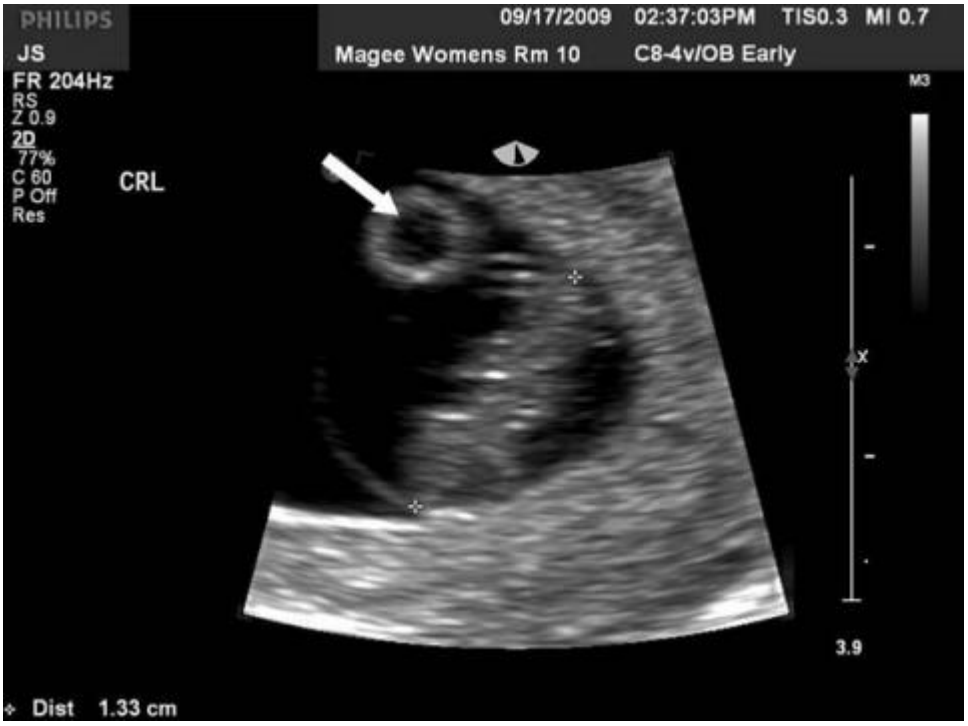

Figure 8 - Normal yolk sac (arrow) at 7.5 weeks' menstrual age.

The maximum diameter of the yolk sac is approximately 6 mm at 10 weeks' menstrual age[33].
Yolk sac vascularity is characterized by a low velocity and absence of diastolic flow. The gradual decline in yolk sac function after 9 weeks' menstrual age coincides with a progressive decrease in yolk sac vascularity just as the placenta takes over the metabolic demands of a rapidly growing embryo[34].
There are reports of yolk sac diameters > 7 mm being associated with embryonic demise (Fig. 9)[35]. Other studies have not found a significant correlation between yolk sac diameter and embryonic outcome[36].
The yolk sac is normally circular. An abnormal yolk sac shape has a poor sensitivity (29%) and a 47% positive predictive value for predicting miscarriage[37]. An abnormality in yolk sac size or shape is due to poor embryonic development or demise rather than being the primary cause of a 1st trimester loss. An impairment in calcium transport leads to an accumulation of calcium in the yolk sac. A calcified yolk sac without blood flow is, therefore, indicative of a long standing embryonic demise (Fig. 10)[34].

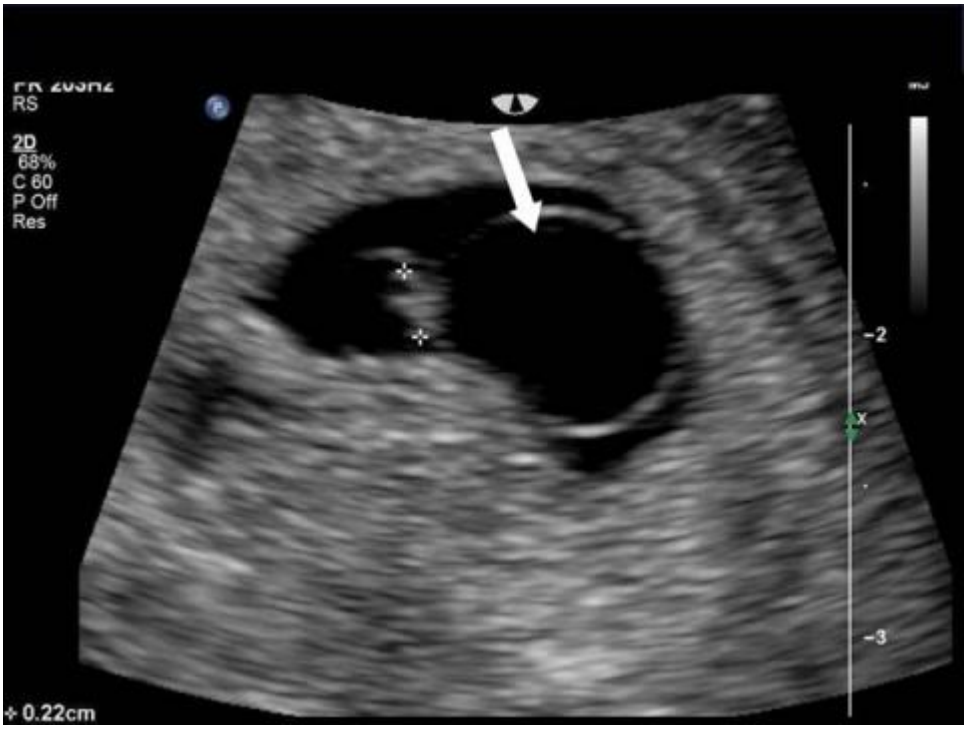

Figure 9 - Embryonic demise with an enlarged yolk sac (arrow).

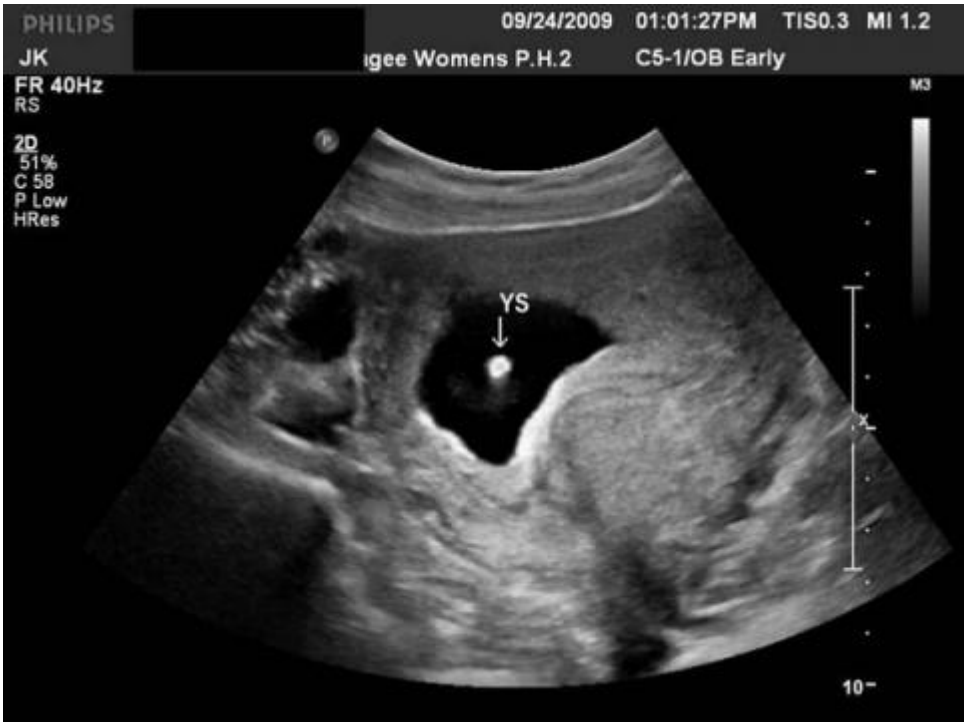

Figure 10 - Calcified yolk sac (ys) with an embryonic demise of 2 weeks.

CROWN-RUMP LENGTH

Variations in ovulation, fertilization or implantation may explain some of the differences found in crown-rump lengths of specific gestational ages. As a result, crown-rump length dating tables using optimal menstrual history tend to underestimate gestational age by 2 to 3 days when compared to tables constructed from patients with a known conception date[38]. Once growth begins, normal embryos have similar growth curves[39].

The embryo is present from 9 days after conception. The embryonic period begins at 3 weeks after conception (5 weeks' menstrual age) and continues until organogenesis is complete (8 weeks after conception; 10 weeks' menstrual age)[19]. The fetal period begins after 10 weeks' menstrual age and is a

period of differentiation and growth, not development.
Until the embryo is 4 mm, it is straight and the measurement obtained is actually the longest visible length. After a crown-rump length of 4 mm, there is rapid head growth and the body begins to curve. Hence, a crown-rump length measurement is actually a “neck-rump” length (Fig. 11). By 7 weeks and 3 days menstrual age the embryonic head and body can be distinguished[40]. By 18 mm (8 weeks’ menstrual age) a true crown-rump length measurement can be obtained (Fig. 12)[41].

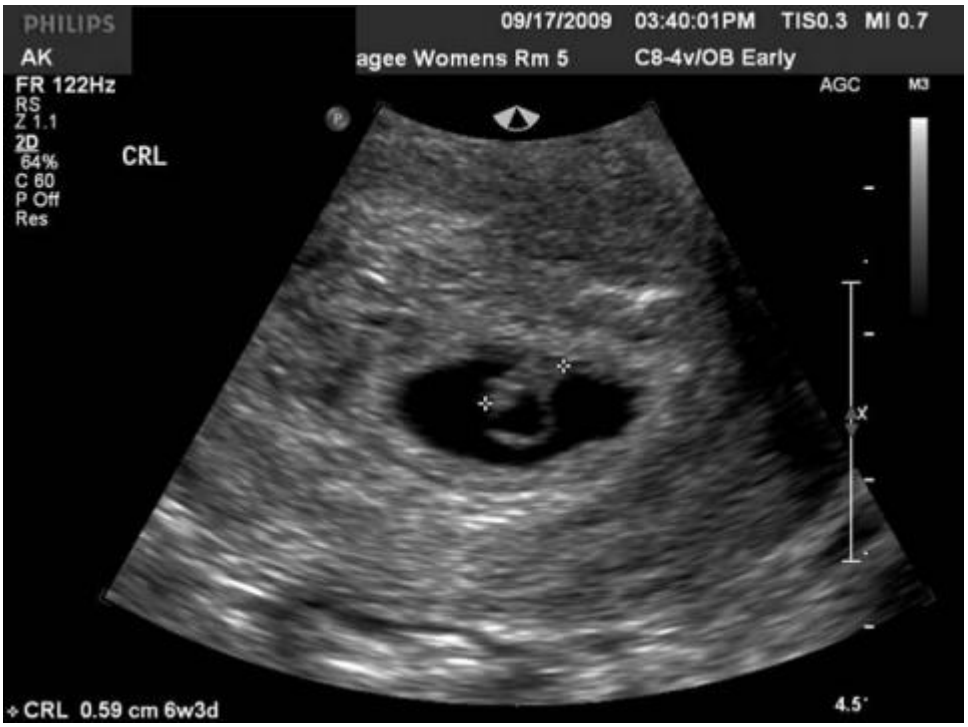

Figure 11 - “Neck-rump” length of 0.59 cm at 6.2 weeks’ menstrual age.

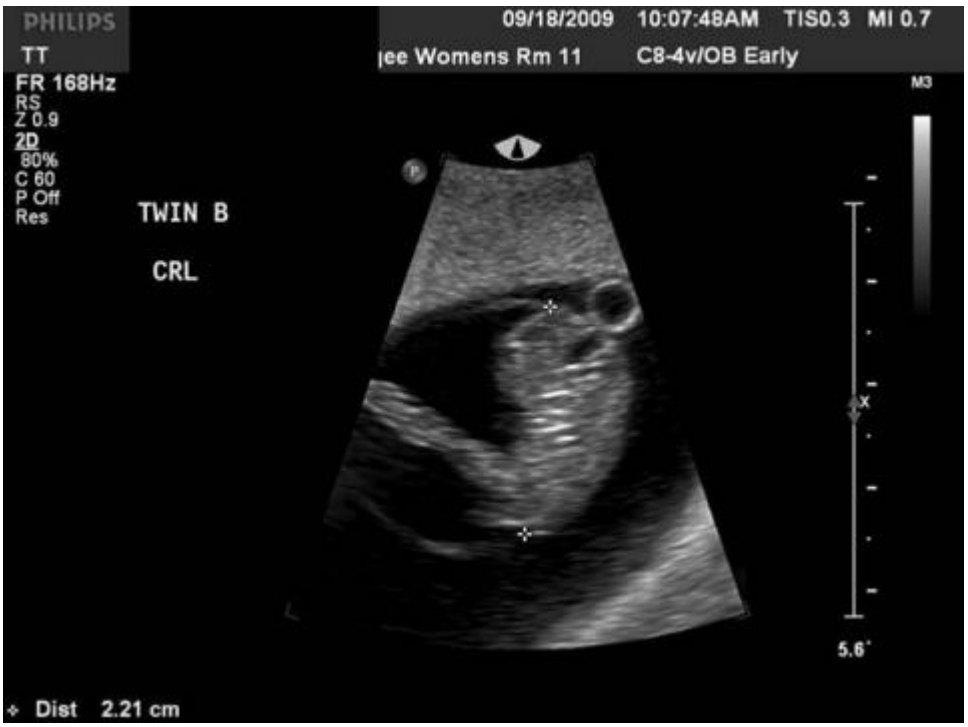

Figure 12 - Crown-rump measurement at 8.9 weeks’ menstrual age.

The crown-rump length in the early part of the 1st trimester increases by at least 0.9 mm per day.

Hence, with normal growth, a change in embryo size can be observed in 2 days. The crown-rump length is reported to have a variability of ± 5-7 days in 95% of cases. Others have reported a 95% reference interval of ± 8.6 days[24]. Hadlock et al[42] estimated the 95% confidence interval of a crown-rump length to be ± 8%.

CARDIAC ACTIVITY

Embryonic cardiac activity can be documented by transvaginal sonography at a menstrual age of 5 weeks and 1 day. Hence, cardiac activity should be present when the embryo is > 2 mm. However, in 5-10% of normal embryos cardiac activity is not visualized between 2 and 4 mm[43,44].Embryonic cardiac activity should be identified with a crown–rump length > 7 mm [44b]. In order to minimize error, the diagnosis of an embryonic demise should not be made on a single visit, only on a follow-up examination [44c].

Embryonic cardiac activity is initially quite slow (82 to 101 beats per minute at 5 weeks' menstrual age)(Fig. 13)[45,46]. The rate increases as the atrium initiates its pacemaker function. The heart rate increases by approximately 4 beats per minute per day[46]. The increase in heart rate is required to increase cardiac output for a growing embryo[47].

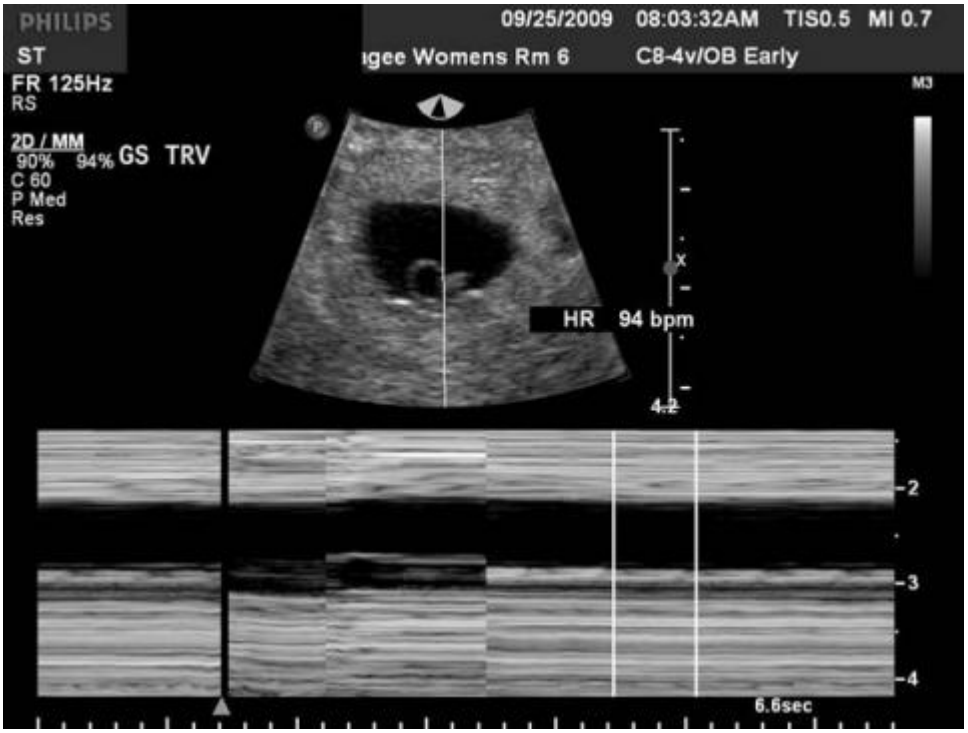

Figure 13 - Normal embryonic heart rate (94 bpm) at 5.6 weeks' menstrual age.

Both maternal history and sonographic findings affect the fetal loss rate after detecting cardiac activity at 6-10 weeks' menstrual age. For example, the incidence of embryonic loss after visualizing cardiac activity at 6-10 weeks increases from 4% at 20 years of age to 20% for women > 35 years old. As one would expect the miscarriage rate decreases with advancing gestation from 10% at 6 weeks to 3% at 10 weeks. First trimester vaginal bleeding increases the miscarriage rate by 2.6-fold[48].

The three sonographic parameters that have been shown to have an association with embryonic success or failure include; appropriate gestational sac size, an appropriate crown-rump length for gestational age, and embryonic heart rate. Embryonic bradycardia is a poor prognostic sign[49]. A single observation of an embryonic heart rate < 80 beats per minute at 7 weeks' menstrual age has a 70% sensitivity and 94%

positive predictive value for an embryonic demise. The false positive rate of an embryonic bradycardia was documented by Merchiers et al[45] who reported a case of transient bradycardia of 48 beats per minute that resulted in a normal pregnancy outcome. The embryonic demise rate between 6 and 7.1 weeks' menstrual age increased as the initial heart rate falls[50] and decreases as the heart rate rises. Doubilet and Benson[51] reported a 60.6% 1st trimester demise rate with an embryonic bradycardia between 6-7 weeks' menstrual age. If on a subsequent exam at 8 weeks' gestation, the heart rate was normal, the demise rate was reduced by 25.4%. Even the latter result was significantly increased over the 7.2% demise rate in a control group with a normal embryonic heart rate. If a pregnancy with an embryonic bradycardia survives the 1st trimester, the loss rate during the remaining months of pregnancy is quite low[52]. However, the prevalence of structural and chromosomal anomalies is increased from 2.4% in controls to 5.4% in a group with an initial embryonic bradycardia who survive[53]. In contrast to an embryonic bradycardia, an embryonic tachycardia (? 135 bpm before 6.3 weeks' menstrual age and ? 155 bpm between 6.3-7 weeks' menstrual age) is not associated with an increase in miscarriage rate[54].

The favorable outcome associated with the detection of a normal embryonic heart rate (Table I) cannot be used with a history of recurrent miscarriage. In this high-risk group miscarriage or fetal death rates after documenting cardiac activity is approximately 17%[55]. Both gestational sac and embryonic growth are initially normal, but become abnormal prior to demise[56]. When both the mean gestational sac diameter and the crown-rump length are smaller then expected, Nazari et al[57] found a 71% miscarriage rate with 3.5% false positive rate.

Table I. Miscarraige rate based on sonographic landmark obtained.

Sonographic Landmark	Miscarriage Rate (%)
Gestational sac	11.5
Yolk sac	8.5
5 mm embryo	7.2
6-10 mm embryo	3.3
> 10 mm embryo	0.5

Derived from Goldstein SR. Obstet Gynecol 1992;80:670.

In some cases an embryonic bradycardia may be due to an underlying chromosomal abnormality[58]. However, the prevalence of karyotypic abnormalities with an embryonic bradycardia is the same as for spontaneous 1st trimester miscarriages in general[59].

DEVELOPMENTAL LANDMARKS

The sonographic appearance of developmental landmarks in early pregnancy occurs within well-defined gestational age time periods. A gestational sac and embryonic cardiac activity should be visualized in 95% of cases by 5.6 weeks and 6.6 weeks' menstrual age, respectively[60]. The association between sonographic landmarks and subsequent miscarriage are outlined on Table I. Table II provides the menstrual age at which specific embryonic landmarks are detectable sonographically during organogenesis (weeks 5 to 10 menstrual age). The single cavity within the head visualized at 7 weeks' menstrual age is the rhombencephalon (Fig. 14)[40].

Table II.

Menstrual Age (weeks)	Sonographic Landmark

4	Gestational sac without yolk sac
5	Yolk sac present
6	Embryonic cardiac activity
7	Single ventricle without a falx
9	Falx visualized; mid-gut herniation; limb movements

Derived from:
Warren WB et al. Am J Obstet Gynecol 1989;161:747.
Timor-Tritsch IE et al. Am J Obstet Gynecol 1988;159:676-681.

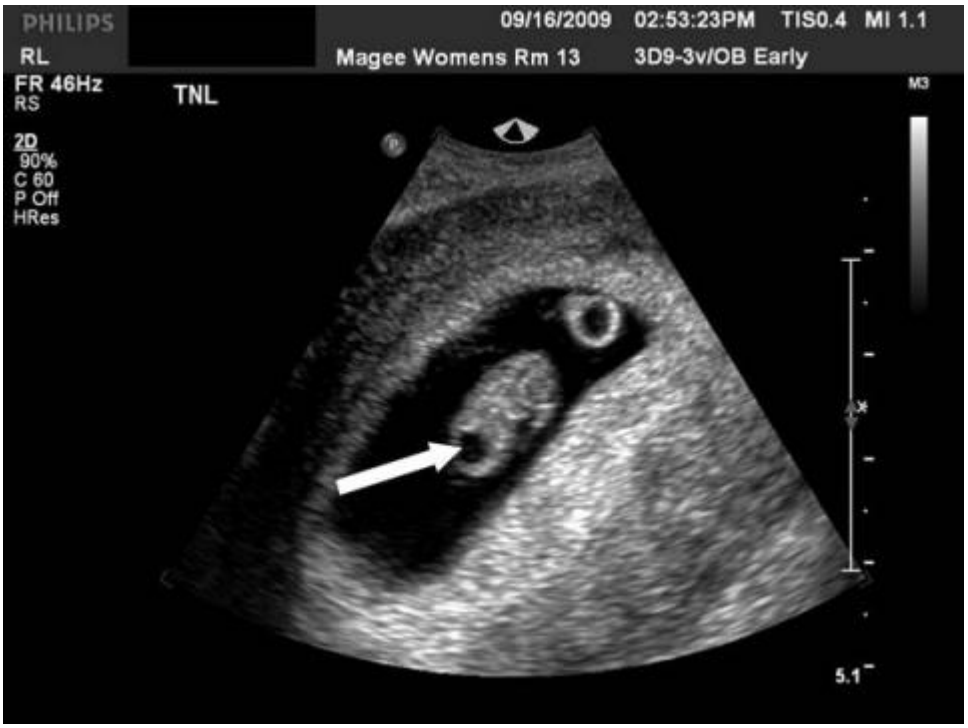

Figure 14 - The single cavity (arrow) present in the fetal head is the rhombencephalon.

THREATENED MISCARRIAGE

Vaginal bleeding prior to 6 weeks' menstrual age has not been associated with an increased risk of miscarriage[61]. However, 1st trimester vaginal bleeding between 7 and 12 weeks' menstrual age is associated not only with a 5-10% miscarriage rate, but also a higher risk of premature rupture of the membranes and pre-term labor[62]. The risk of miscarriage is directly related to the severity of vaginal bleeding. In the FASTER trial evaluation of 1st trimester bleeding, the odds ratio for subsequent miscarriage was 2.5 for patients with light vaginal bleeding, in contrast to an odds ratio of 4.2 in patients with heavy vaginal bleeding[62].

In patients with 1st trimester vaginal bleeding, a retroplacental hematoma, in contrast to a marginal subchorionic hemorrhage is more predictive of subsequent miscarriage[13].

There is not a direct relationship between the size of a subchorionic hematoma and outcome[63].

A “chorionic bump” (Fig. 15) is a small hematoma that protrudes into the gestational sac. This sonographic finding in one study was associated with a live birth rate of < 50%[64].

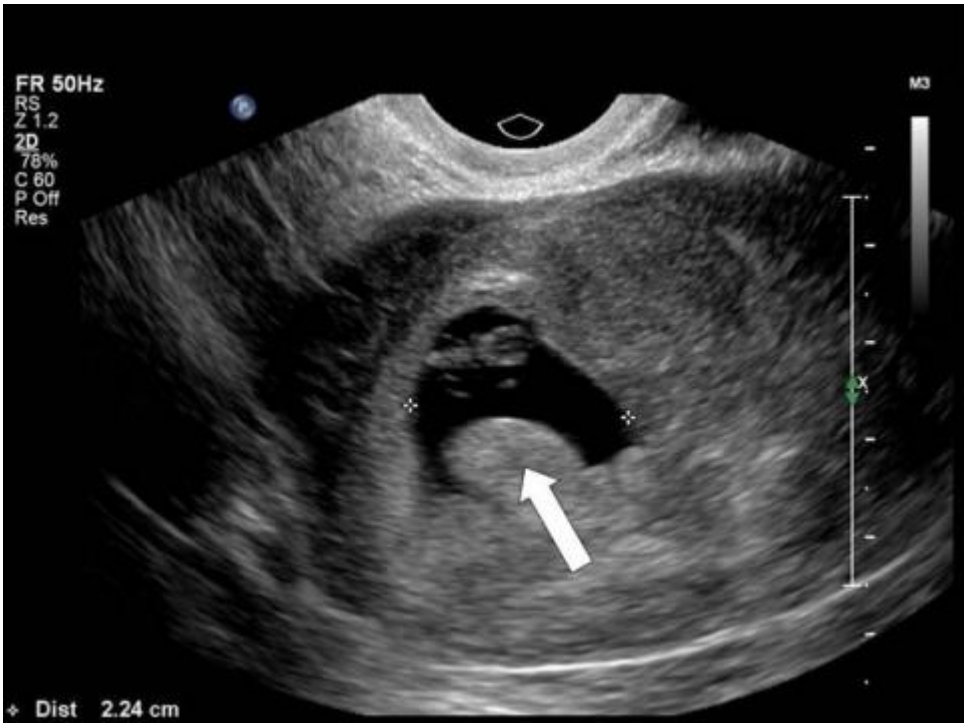

Figure 15 - Chorionic bump (arrow) protruding into a gestational sac.

Seventy percent of 1st trimester miscarriages are chromosomally abnormal, of which 60% are autosomal trisomies59.
An incomplete miscarriage results in a heterogeneously thickened endometrial lining.
In one study expectant management for an incomplete miscarriage was significantly better than for a missed miscarriage[65]. Medical management with misoprostol may be as effective as surgical management for an incomplete miscarriage.

HYDATIDIFORM MOLE

A complete hydatidiform mole has a 46 xx chromosomal pattern with all of the chromosomes of paternal origin. One percent of complete moles are associated with a viable fetus because of a twin dizygotic gestation (i.e. a complete mole and a normal pregnancy)[16].
The classic complete hydatidiform mole has a “swiss cheese” sonographic appearance representing the hydropic villi[66]. The size of the villi is correlated with gestational age64. Hence, in the 1st trimester only 50% of complete hydatidiform moles have a classic appearance (Fig. 16). The remaining cases may present as an anembryonic gestational sac or thick endometrium without the classic vesicles[66,67].
Excessive hCG production results in 2nd or 3rd trimester theca lutein cysts. In the 1st trimester the hCG level is low to normal for gestational age in two-thirds of cases[62]. Hence, theca lutein cysts are uncommon[68].

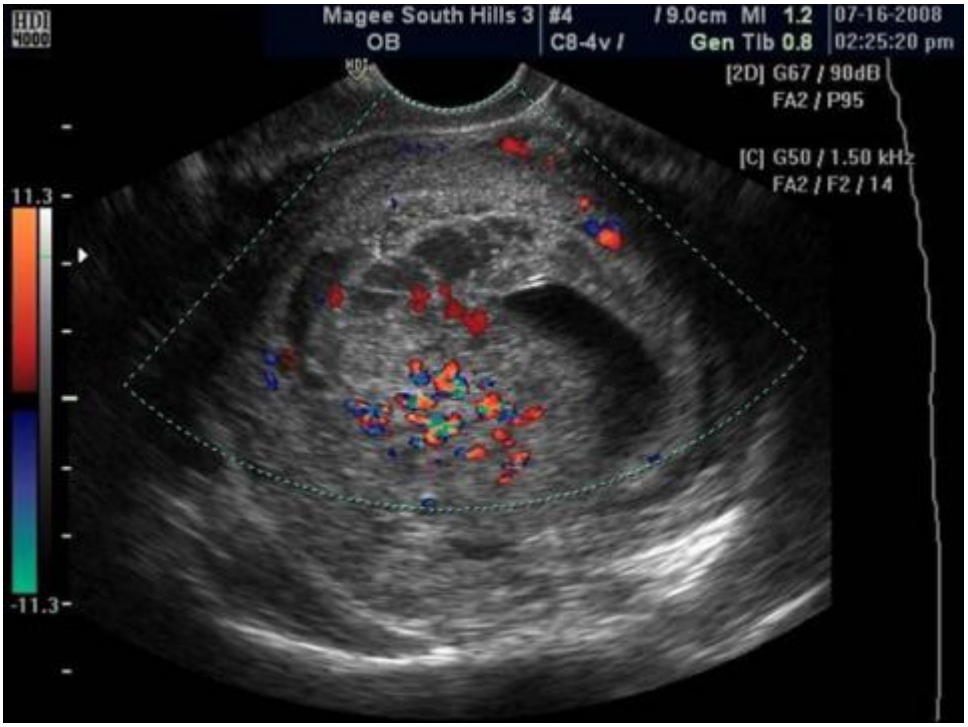

Figure 16 - 1st trimester hydatidiform mole.

A partial more is due to triploid (69, xxy) or rarely tetraploidy (92, xxxy). A gestational sac with an embryonic pole is present. The placenta is enlarged and contains hydropic villi[68].
Hydropic changes in an early embryonic demise may look sonographically identical to a hydatidiform mole[69].

CONCLUSION

Familiarity with normal embryological development, sonographic landmarks, and appropriate hCG levels provides the observer with the necessary tools to assess, not only normal development, but also pathologic conditions that occur in the 1st trimester.

REFERENCES

1. Basir GS, O WS, So WS, Ng EH, Ho PC. Evaluation of cycle-to-cycle variation of endometrial responsiveness using transvaginal sonography in women undergoing assisted reproduction. Ultrasound Obstet Gynecol 2002;19:484-489.
2. Yang JH, Wu MY, Chen CD, Jiang MC, Ho HN, Yang YS. Association of endometrial blood flow as determined by a modified colour Doppler technique with subsequent outcome of in-vitro fertilization. Hum Reprod 1999;14:1606-1610.
3. Gergely RZ, DeUgarte CM, Danzer H, Surrey M, Hill D et al. Three-dimensional/four-dimensional ultrasound-guided embryo transfer using the maximal implantation potential points. Fertil Steril 2005;84:500-503.
4. Kawakami Y, Andoh K, Mizunuma H, Yamada K, Itoh M, Ibuki Y. Assessment of the implantation site by transvaginal ultrasonography. Fertil Steril 1993;59:100-31006.
5. Habara T, Nakatsuka M, Konishi H, Asagiri K, Noguchi S, Kudo T. Elevated blood flow resistance in uterine arteries of women with unexplained recurrent pregnancy loss. Hum Reprod 2002;17:190-194.
6. James SL, Stone PR, Chamley LW. The regulation of trophoblast differentiation by oxygen in the first trimester of pregnancy. Hum Reprod Update 2006;12:137-144.

7. Jauniaux E, Johns J, Burton GJ. The role of ultrasound in diagnosing and investigating early pregnancy failure. Ultrasound Obstet Gynecol 2005;25:613-624.
8. Burton GJ, Jauniaux ER, Watson Al. Maternal arterial connection to the placental intervillous space during the first trimester of pregnancy: The Boyd collection revisited. Am J Obstet Gynecol 1999;181:718-724.
9. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress – a possible factor in human early pregnancy failure. Am J Pathol 2000;157:2111-2122.
10. Abramovich DR. The volume of amniotic fluid in early pregnancy. J Obstet Gynaecol Br Commonw 1968;73:728-731.
11. Merce LT, Barco MJ, Bau S. Color Doppler sonographic assessment of placental circulation in the first trimester of normal pregnancy. J Ultrasound Med 1996;15:135-142.
12. Jauniaux E, Greenwald N, Hempstock J, Burton GJ. Comparison of ultrasonographic and Doppler mapping of the intervillous circulation in normal and abnormal early pregnancies. Fertil Steril 2003;79:100-106.
13. Alkazar JL, Ruiz-Perez ML. Uteroplacental circulation in patients with first-trimester threatened abortion. Fertil Steril 2000;73:130-135.
14. Bree RL, Edwards M, Bohm-Velez M, Beyler S, Roberts J, Mendelson EB. Transvaginal sonography in the evaluation of normal early pregnancy: correlation with HCG level. AJR 1989;153:75-79.
15. Nyberg DA, Laing FC, Filly RA. Threatened abortion: sonographic distinction of normal and abnormal gestation sacs. Radiol 1986;158:397-400.
16. Dogra V, Paspulati RM, Bhatt S. First trimester bleeding evaluation. US Quarterly 2005;21:69-85.
17. Reece EA, Pinter E, Leranth C, Hobbins JC, Mahoney MJ, Naftolin F. Yolk sac failure in embryopathy due to hyperglycemia: horseradish peroxidase uptake in the assessment of yolk sac function. Obstet Gynecol 1989;74:755-762.
18. Goldstein SR. Early detection of pathologic pregnancy by transvaginal sonography. J Clin Ultrasound 1990;18:262-273.
19. Goldstein SG. Early pregnancy. Semin Reprod Med 2008;26:277-284.
20. Kadar N, Devore G, Romero R. Discriminating hCG zones: Its use in the sonographic evaluation of ectopic pregnancy. Obstet Gynecol 1981;58:156-161.
21. Barnhart K, Mennuti MT, Benjamin I, Jacobson S, Goodman D, Coutifaris C. Prompt diagnosis of ectopic pregnancy in an emergency department setting. Obstet Gynecol 1994;84:1010-1015.
22. Shapiro BS, Escobar M, Makuch R, Lavy G, DeCherney AH. A model-based prediction for transvaginal ultrasonographic identification of early intrauterine pregnancy. Am J Obstet Gynecol 1992;166:1495-1500.
23. Jurkovic D, Gruboeck K, Campbell S. Ultrasound features of normal early pregnancy development. Curr Opin Obstet Gynecol 1995;7:493-504.
24. Grisolia G, Milano V, Pilu G, Banzi C, David S et al. Biometry of early pregnancy with transvaginal sonography. Ultrasound Obstet Gynecol 1993;3:403-411.
25. Bromley B, Harlow BL, Laboda LA, Benacerraf BR. Small sac size in the first trimester: a predictor of poor fetal outcome. Radiology 1991;178:375-377.

26. Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationship of small gestational sac-crown-rump length differences to miscarriage and abnormal karyotypes. Obtet Gynecol 1992;79:554-557.
27. Rempen A. Diagnosis of viability in early pregnancy with vaginal sonography. J Ultrasound Med 1990;9:711-716.
28. Elson J, Salim R, Tailor A, Banerjee S, Zosmer N, Jurkovic D. Prediction of early pregnancy viability in the absence of an ultrasonically detectable embryo. Ultrasound Obstet Gynecol 2003;21:57-61.
29. Luise C, Jermy K, Collins WP, Bourne Th. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ 2002;324:873-875.
30. Jauniaux E, Gulbis B, Jurkovic D, Gavriil P, Campbell S. the original of alpha- fetroprotein in firstr-trimester anembryonic pregnancies. Am J Obstet Gynecol 195;173:1749-1753.
31. Horrow MM. Enlarged amniotic cavity: A new sonographic sign of early embryonic death. AJR 1992;158:359-362.
32. McKenna KM, Feldstein VA, Goldstein RB, Filly RA. The “empty amnion”: a sign of early pregnancy failure. J Ultrasound Med 1995;14:117-121.
33. Jauniaux E, Jurkovic D, Henriet Y. Development of the secondary human yolk sac: correlation of sonographic and anatomic features. Hum Reprod 1991;6:1160-1165.
34. Kurjak A, Kupesic S. Parallel Doppler assessment of yolk sac and intervillous circulation in normal pregnancy and missed abortion. Placenta 1998;19:619-623.
35. Cepni I, Bese T, Ocal P, Budak E, Idil M, Aksu F. Significance of yolk sac measurements with vaginal sonography in the first trimester in the prediction of pregnancy outcome. Acta Obstet Gynecol Scand 1997;76:969-972.
36. Kurtz AB, Needleman L, Pennell RG. Can detection of the yolk sac in the first trimester be used to predict the outcome of pregnancy? A prospective sonographic study. AJR 1992;158:843-846.
37. Küçük T, Duru NK, Yenen MC, Dede M, Ergün A, Ba?er I. Yolk sac size and shapes as predictors of poor pregnancy outcome. J Perinat Med 1999;27:316-330.
38. MacGregor SN, Tamura RK, Sabbagha RE, Minogue JP, Gibson ME, Hoffman DI. Underestimation of gestational age by conventional crown-rump length dating curves. Obstet Gynecol 1987;70:344-348.
39. Blaas H-G, Eik-Nes SH, Bremnes JB. The growth of the human embryo. A longitudinal biometric assessment from 7 to 12 weeks of gestation. Ultrasound Obstet Gynecol 1998;12:346-354.
40. Blaas HG, Eik-Nes SH, Kiserud T, Hellevik LR. Early development of the hind brain: a longitudinal ultrasound study from 7 to 12 weeks of gestation. Ultrasound Obstet Gynecol 1995;5:151-158.
41. Goldstein S. Embryonic ultrasonographic measurements: crown-rump length revisited. Am J Ostet Gynecol 1991;165:497-499.
42. Hadlock FP, Shah, YP, Kanon DJ, Lindsey JV. Fetal crown-rump length: re-evaluation of relation to menstrual age (5-18 weeks) with high-resolution real-time US. Radiology 1992;182:501-505.
43. Levi CS, Lyons EA, Zheng XH, Lindsay DJ, Holt SC. Endovaginal US: Demonstration of cardiac activity in embryos of less than 5.0 mm in crown-rump length. Radiol 1990;176:71-74.
44. Goldstein SR. Significance of cardiac activity on endovaginal ultrasound in early embryos. Obstet Gynecol 1992;80:670-672.
    2. Abdullah Y, Daemon A, Kirk E, Pexsters A, Naji O, Stalder C, Gould D, Bourne T. Limitations of current definitions of miscarriage using mean gestational sac diameter and crown-rump length

measurements: a multicenter observational study. Ultrasound Obstet Gynecol 2011; 38: 497-502.

3. Hately W, Case J, Campbell S. Establishing the death of an embryo by ultrasound: report of a public inquiry with recommendation. Ultrasound Obstet Gynecol 1995; 5: 353-357.

45. Merchiers EH, Dhont M, DeSutter PA, Beghin CJ, Vandekerckhovc DA. Predictive value of early embryonic cardiac activity for pregnancy outcome. Am J Obstet Gynecol 2991;165:11-14.
46. Tezuka N, Sato S, Kanasugi H, Hiroi M. Embryonic heart rates: Development in early first trimester and clinical evaluation. Gynecol Obstet Invest 1991;32:210-212.
47. Jauniaux E, Jurkovic D, Campbell S. In vivo investigations of the anatomy and the physiology of early human placental circulations. Ultrasound Obstet Gynecol 1991;1:435-445.
48. Makrydimos G, Sebire NJ, Lolis D, Vlassis D, Vlassis N, Nicolaides KH. Fetal loss following ultrasound diagnosis of a live fetus at 6-10 weeks of gestation. Ultrasound Obstet Gynecol 2003;22:368-372.
49. Laboda LA, Estroff JA, Benacerraf BR. First trimester bradycardia. A sign of impending fetal loss. J Ultrasound Med 1989;8:561-563.
50. Benson CB, Doubilet PM. Slow embryonic heart rate in early first trimester: indicator of poor pregnancy outcome. Radiology 1994;192:343-344.
51. Doubilet PM, Benson CB. Outcome of first-trimester pregnancies with slow embryonic heart rate at 6-7 weeks' gestation and normal heart rate by 8 weeks at ultrasound. Radiology 2005;236:643-646.
52. Chittacharoen A, Herabutya Y. Slow fetal heart rate may predict pregnancy outcome in first-trimester threatened abortion. Fertil Steril 2004;82:227-229.
53. Doubilet PM, Benson CB, Chow JS. Long-term prognosis of pregnancies complicated by slow embryonic heart rates in the early first trimester. J Ultrasound Med 1999;18:537-541.
54. Doubilet PM, Benson CB, Chow JS. Outcome of pregnancies with rapid embryonic heart rates in the early first trimester. AJR 2000;175:67-69.
55. VanLeeuwen I, Branch DW, Scott JR. First-trimester ultrasonography findings in women with a history of recurrent pregnancy loss. Am J Obstet Gynecol 1993;164:111-114.
56. Cunningham DS, Bledsoe LD, Tichenor JR, Opsahl MS. Ultrasonographic characteristics of first-trimester gestations in recurrent spontaneous aborters. J Reprod Med 1995;40:565-570.
57. Nazari A, Check JH, Epstein RH, Dietterich C, Farzanfar S. Relationship of small-for-dates sac size to crown-rump length and spontaneous abortion in patients with a known date of ovulation. Obstet Gynecol 1991;78:369-373.
58. Liao AW, Snijders R, Geerts L, Spencer K, Nicolaides KH. Fetal heart rate in chromosomally abnormal fetuses. Ultrasound Obstet Gynecol 2000;16:610-613.
59. Ohno M, Maeda T, Matsunobo A. A cytogenetic study of spontaneous abortions with direct analysis of chorionic villi. Obstet Gynecol 1991;77:394-398.
60. Goldstein I, Zimmer EA, Tamin A, Peretz A, Paldi E. Evaluation of normal gestation sac growth: appearance of embryonic heartbeat and embryo body movement using the transvaginal technique. Obstet Gynecol 1995;77:885-887.
61. Harville EW, Wilcox AJ, Baird DD, Weinberg CR. Vaginal bleeding in very early pregnancy. Hum Reprod 2003;18:1944-1947.
62. Weiss JL, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH et al. Threatened abortion: a risk

factor for poor pregnancy outcome, a population-based screening study. Am J Obstet Gynecol 2004;190:745-750.

63. Pedersen JF, Mantoni M. Prevalence and significance of subchorionic hemorrhage in threatened abortion: a sonographic study. AJR 1990;154:535-537.
64. Harris RD, Couto C, Karpovsky C, Porter MMB, Ouhilal S. The Chorionic Bump. A first-trimester pregnancy sonographic finding with a guarded prognosis. J Ultrasound Med 2006;25:757-763.
65. Siram S, Khare M, Michalidis G, Thilaganathan B. The role of ultrasound in the expectant management of early pregnancy loss. Ultrasound Obstet Gynecol 2001;17:506-509.
66. Lazarus E, Hulka CA, Stewart B, Levine D. Sonographic appearance of early complete molar pregnancies. J Ultrasound Med 1999;18:589-593.
67. Benson CB, Genest DR, Bernstein MR, Soto-Wright V, Goldstein DP, Berkowitz RS.. Sonographic appearance of first trimester complete hydatidiform moles. Ultrasound Obstet Gynecol 2000;16:188-191.
68. Dighe M, Cuevas C, Moshiri M, Dubinsky T, Dogra VS. Sonography in first trimester bleeding. J Clin Ultrasound 2008;36:352-366.
69. Sawyer E, Jurkovic D. Ultrasonography in the diagnosis and management of abnormal early pregnancy. Clin Obstet Gynecol 2007;50:31-54.