1 Early pregnancy loss

Most perinatologists deal more frequently with patients during the second portion of the first trimester, and I am no exception. For that reason, while drafting this chapter I needed help with the topics of early pregnancy milestones and the common problem of early first trimester embryonic/fetal loss. After a brief search, I came up with a gem in the form of syllabus material accompanying a superb lecture by Dr Steven Goldstein, given at an ultrasound course. This will be sprinkled throughout this chapter.

Early pregnancy can be divided up into three segments: the pre-embryonic period (conception to 5 menstrual weeks); the embryonic period, during which time organogenesis is the major activity (4–9 menstrual weeks); and the early developmental period, during which time the fetus simply grows while adding to the building blocks formed earlier (10–12 weeks). Not surprisingly, the third segment has been called the fetal period.

Ultrasound milestones

First, it must be stipulated that there is a major difference between when a certain finding *can* appear and when it *should* be present, the latter having more importance in early pregnancy failure. Also, one can identify structures much earlier with transvaginal ultrasound, which has a separate timetable. Frankly, up until the eleventh week, there is little reason to view a first trimester pregnancy with transabdominal ultrasound (TAU) other than as an initial quick scouting venture.

The first ultrasound sign of pregnancy is a gestational sac that is generally oblong and has a thick "rind" (Figure 1.1a). The sac should have a double ring, representing the decidua capsularis and the decidua parietalis, and should be seen when the beta human chorionic gonadotropin (hCG) is between 1000 and 2000 mIU/mL. Once seen, the sac diameter should grow by an average of 1 mm a day, and the mean sac diameter (MSD) can be used as a gauge against which to assess other findings [1]. Beware of the pseudosac, which does not have a double ring and is seen in association with ectopic pregnancy (Figure 1.1b).

The yolk sac is the second structure to be visible by ultrasound (Figure 1.2). It can be seen when the MSD is 5 mm, but it *should* be seen by the time the MSD is 8 mm [2]. It plays a crucial role in the development of the fetus—providing nourishment and producing the stem cells that develop into red blood cells, white blood cells, and platelets. In effect, the yolk sac provides the immunological potential for the fetus until about 7 menstrual weeks, when those functions are taken over by the fetal liver. From then on the functionless yolk sac becomes a circular structure without a core, after which it finally disappears by 12 menstrual weeks.

After about 8 weeks, the yolk sac has little diagnostic value and, although some studies have suggested that a macro yolk sac (more than 6 mm) is an ominous sign, our own observations have not borne this out. We have noted a "filled in" yolk sac (Figure 1.3) to be sometimes associated with fetal demise, but in these cases the embryo/fetus provides the ultimate information.

One can see an embryo by 5 menstrual weeks and a way to determine gestational age is to add 42 days to the crown–rump length (CRL) measurement in millimeters. The embryo should increase its CRL by 1 mm/d. Not seeing an embryo when the MSD has reached 6 mm is indicative of a pregnancy loss [3]. Also, the size of the embryo, relative to the MSD, is important. For example, if the MSD–CRL is <6 mm, the prognosis is very poor.

Cardiac activity should be visualized when the embryonic length is greater than or equal to 4 mm, and not seeing a beating heart at this embryonic size is an ominous sign [4]. The heart rate itself may provide insight into the fate of the pregnancy. For example, Benson and Doubilet [5] noted that if the heart rate (HR) was less than

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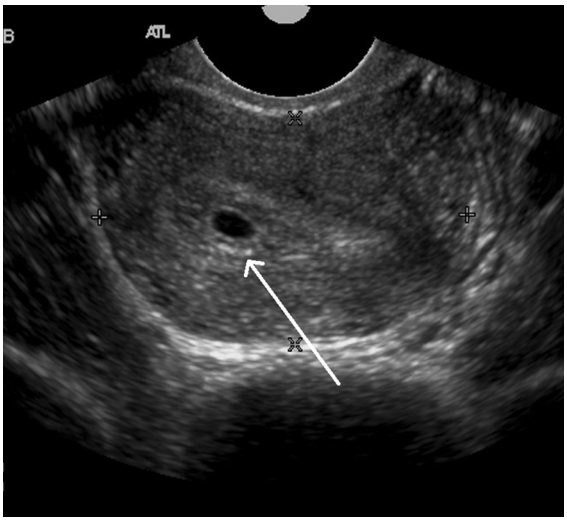
(a)



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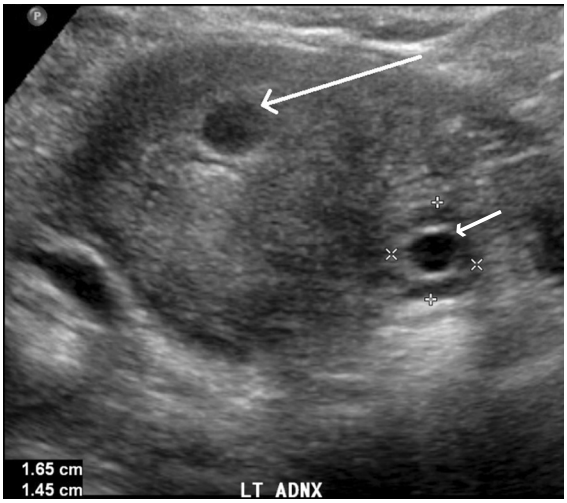

Fig 1.1 (a) Early gestational sac. (b) Ectopic. Large arrow points to pseudosac. Small arrow points to ectopic next to uterus.

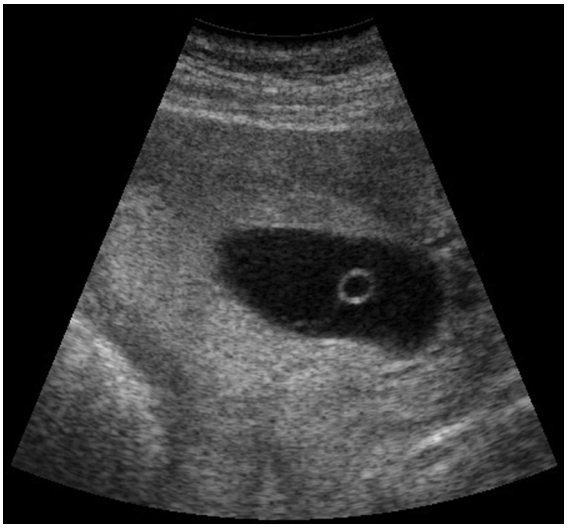

Fig 1.2 Yolk sac.

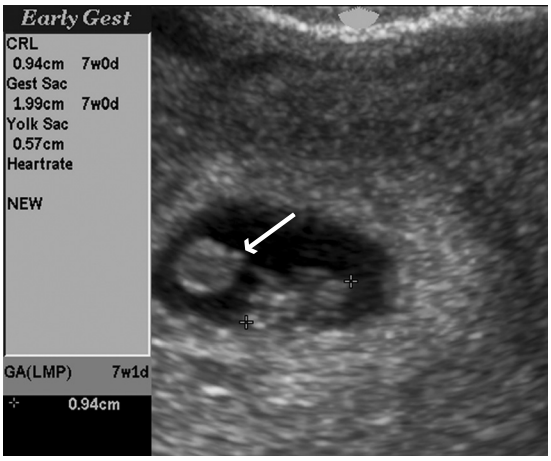

Fig 1.3 Filled-in yolk sac; calipers are on CRL and arrow points to yolk sac.

90 in pregnancies that were less than 8 weeks, there was an 80% chance of fetal death. If the HR was below 70, 100% ultimately had an intrauterine demise. Later in the first trimester, fetuses with HR above the 95th percentile have a markedly increased risk for trisomy 13 [6].

Human chorionic gonadotropin (hCG)

This is a product of the placenta that rises linearly throughout the first trimester and decreases through the second trimester. Although various investigators have explored subunits of the hCG molecule in screening for Down syndrome (beta subunit), the assays commonly used today for standard monitoring of early pregnancy measure intact hCG (not beta hCG).

Should see on TVS	Time of visualization
Gestation sac	5 menstrual weeks
Yolk sac	when MSD is >7mm
Embryonic pole	5 weeks or when hCG is >1000 mIU
Fetal heart activity	when CRL is >5 mm

Initially, Kadar et al. [7] described a "discriminatory level," above which one should see an embryo (6500 mμ/mL), to help sort out pregnancy loss from ectopic pregnancy. These initial values were based on TAU and an assay that has been replaced by another (second international standard). The hCG level, above which one should identify an embryo by transvaginal sonography, is now 1000 mIU/mL to 2000 mIU/mL, as determined by the second international standard. In a patient clinically at risk for loss or ectopic pregnancy the ideal diagnostic strategy would be to obtain serial measurements of hCG, the levels of which generally double every 48 hours, but certainly should increase by more than 66% in that time period [8].

The natural progression of early pregnancy loss

A surprising number of pregnancies are lost within days of conception. Thereafter, the loss rate diminishes steeply until the twelfth week of gestation. For example, in one study where daily hCG levels were undertaken postconception, 22% of those pregnancies with an initially positive hCG never developed to a point where ultrasound demonstrated a viable pregnancy [8]. In another study from Australia, serum hCG levels were obtained at 16 days postconception in over 1000 patients having had IVF (in vitro fertilization) [9]. The average level was 182 mIU/mL in those with later pregnancy loss (8–19 weeks), compared with 233 mIU/mL in continuing pregnancies [10]. These data again strongly suggest that the die is cast soon after conception for many pregnancy losses. Below, the chances of a continuing pregnancy are laid out according to the ultrasound findings.

Ultrasound findings

When present	Chances of loss before 12 weeks
Gestational sac only	11.5%
Yolk sac only	8.5%
Embryo <6 mm	7.2%
Embryo between 5–10 mm	3.3%
Embryo >10 mm	0.5%

If first trimester bleeding occurs, the loss rates obviously increase. It has been estimated that about 25% of all patients will have some bleeding or spotting in the first trimester, and in half of these pregnancies a viable fetus will not materialize. The most common reason for early loss is aneuploidy. Ohno [11] found that 69.4% of products of conception from 144 spontaneous abortions yielded abnormal chromosomes, the majority representing trisomies. Also, the overwhelming majority of pregnancies are nonviable many days before vaginal bleeding ensues, and the size of the embryo will provide information as to when demise has occurred.

Ectopic pregnancy

The incidence of ectopic pregnancy is about 20/1000, but those with a past history of ectopic pregnancy have a 10-fold greater risk of this complication. Other predisposing factors include pregnancy by assisted reproductive technology (ART), infertility (in general), advanced maternal age, and cigarette smoking.

Identification rates with ultrasound alone range between 20 and 85% [12]. However, using ultrasound in combination with hCG levels improves the positive predictive value to 95% [13].

Since with transvaginal sonography (TVS) it is sometimes difficult to identify an extrauterine pregnancy, the first diagnostic stop should be the uterus. A true gestation sac should be present when the hCG is >2000 mIU/mL, and, in most cases is present when an hCG is >1000 mIU/mL. In general, hCG rises sluggishly in ectopic pregnancy, rarely ever doubling in 48 hours. However, very occasionally a normal early pregnancy will not meet the criteria for an expected rise. Therefore, if no adnexal mass is seen in a patient with symptoms of an ectopic, and the initial hCG level is between 1000 and 2000, a conservative approach might be warranted. On the other hand, if the hCG level is >2000 and no intrauterine sac is identified in a patient with symptoms of ectopic pregnancy, there is a very high likelihood of an extrauterine pregnancy. Obviously, the ultrasound finding of a fetus in the tube or even an adnexal mass should trump any of the above diagnostic subtleties in a symptomatic patient with a positive pregnancy test.

As indicated above, one can be fooled by the "pseudosac" (Figure 1.1b) that masquerades as a true intrauterine sac. It does not have a double ring and is not seen in conjunction with a yolk sac. Also, seeing an intrauterine sac does not completely rule out a heterotopic pregnancy when conception has been accomplished through ART. The prevalence of heterotopic pregnancy has been cited to be about 1 in 30,000, but with ART it could be as high as 1 in 100.

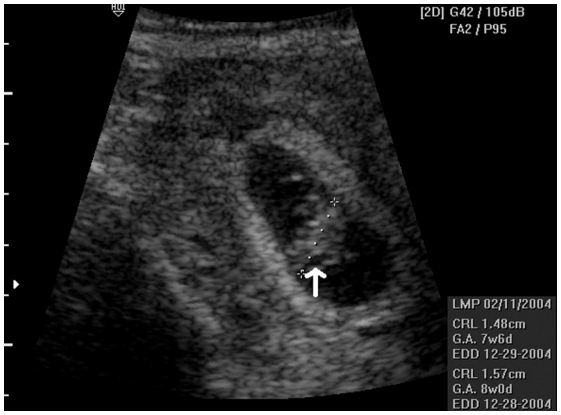

Fig 1.4 Seven-week embryo. Prominent echo-spared area is marked by an arrow.

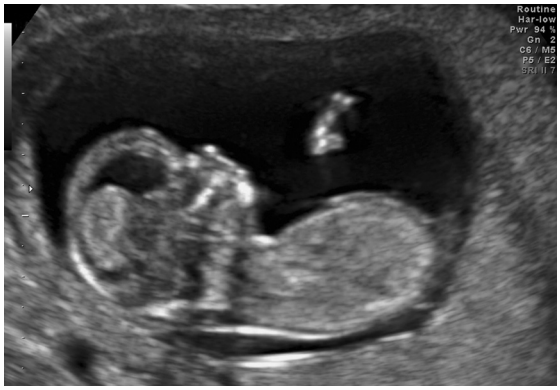

Fig 1.5 Normal first trimester fetus with frontal echo-spared area.

Identification of major fetal abnormalities in the first trimester

In the embryonic stage the organs are just forming so, in general, one must wait until organogenesis is complete and, most importantly, embryos are large enough to visualize, before making diagnostic judgments. An example of an early diagnostic misfire is thinking that an echo-spared structures in the posterior and anterior calvarium (Figures 1.4 and 1.5) before 11 menstrual weeks is an abnormality. With watchful waiting it will become clear that this finding actually represented the normal rhombencephalon that, although visually striking, should not have generated concern.

On occasion, seeing a ventral wall herniation prior to 11 1/2 weeks can raise unwarranted anxiety if one does not realize that this is a normal finding. If the herniation has a wide base, this could represent a true omphalocele, which is, fortunately, a rare finding (Figure 1.6).

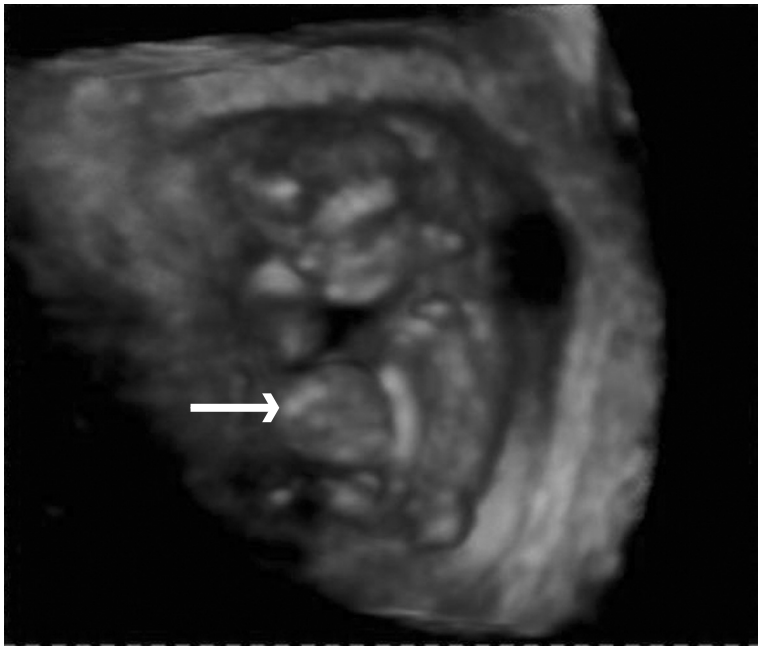

Fig 1.6 3D image of first trimester omphalocele. Arrows points to ventral wall defect.

Table 1.1 Studies in the literature dealing with the identification of anomalies with transvaginal ultrasound. (From Souka AP et al. [14], with permission from Elsevier.)

Author(s)	Population	*N*	Major anomalies (%)	First trimester sensitivity (%)	Total (%)
Hernardi and Torocsik (1997)	Low risk	3991	35 (0.9)	36	72
Economides and Braithwaite (1998)	Low risk	1632	13 (0.8)	54	77
Calvalho et al.	Low risk	2853	66 (2.3)	38	79
Taipale et al.	Low risk	4513	33 (0.7)	18	48
Chen et al.	High risk	1609	26 (1.6)	64	77
Souka et al.	Low risk	1148	14 (1.2)	50	92

Possible false negative observations can also occur. For example, the neural tube closes between 20 and 28 days postconception and a failure of closure early in that window will result in anencephaly. However, since the calvarium is not well mineralized until later in pregnancy, the rudimentary brain will herniate upward and often the fetal cranial pole will appear similar to that of an unaffected fetus. For this reason, in the past a few anencephalic fetuses have evaded diagnosis until after 11 weeks.

In the fetal period, there are now many reports of various fetal abnormalities being identified with 2D and 3D ultrasound, and the nonspecific finding of an increased nuchal translucency (NT) has allowed investigators to search more thoroughly with TVS for anomalies that might ordinarily have been missed.

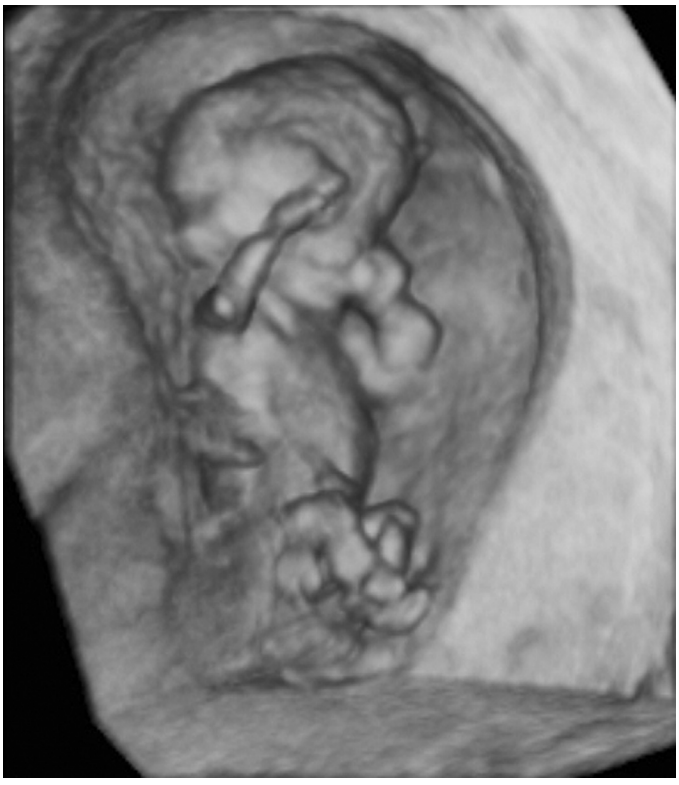

Fig 1.7 First trimester 3D.

Souka et al. [14]. published the results of studies in the literature dealing with the identification of anomalies with transvaginal ultrasound (Table 1.1).

Although 3D ultrasound can provide some beautiful images of the first trimester fetus (Figure 1.7), we utilize this generally useful tool infrequently in the first trimester except to get a better view of the NT when the position of the fetus persistently keeps us from using the necessary midline sagittal approach.

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