REVIEW ARTICLE

Early Pregnancy Scanning: Step-by-Step Overview

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Abstract

Ultrasound is an essential tool for the evaluation of early pregnancy structures. The main method used during early pregnancy is transvaginal ultrasonography, in order to evaluate the course of the pregnancy during the first weeks. Although our knowledge on ultrasound has increased significantly during the last few years, still early pregnancy remains an area with not so well understood findings and structures. In this article, we will review the timeline of the first visualization of the most significant figures, which are expected to be present throughout the first trimester in a normally developing pregnancy. In addition, the suspicious and the diagnostic ultrasound findings of early pregnancy failure will be presented. We will highlight that the diagnosis of early pregnancy failure must be set by following the cutoff values which are established in order to eliminate the possibility of a false positive diagnosis and to avoid any harmful intervention in a viable pregnancy. Finally, we will denote the prognostic predictive value of evaluation of fetal heart rate and subchorionic hematomas presence in early pregnancy. Aim of this article is to review the literature regarding the diagnosis and prognosis of early pregnancies, improve clinicians' knowledge on this issue, and of course to help avoid or decrease possible misdiagnosis.

Keywords: Early pregnancy, Miscarriage, Ultrasound, Yolk sac.

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Introduction—Background

Obstetricians are facing daily in medical practice the challenge to give definite answers about the presence and the viability of a pregnancy. The major role of the first scan performed in women with a positive pregnancy test is to define the location of the implantation and to confirm the viability of the pregnancy.[1] The route preferred for this first scan is the vaginal route, since transvaginal ultrasound can estimate more accurately the pregnancy age in addition with the goals above.[2] The aim of this review article is to present the structures and figures that are expected to be present in a specific timeline throughout a normally developing pregnancy and the diagnostic findings of early pregnancy failure. It is important to be clear that the diagnosis of a failed pregnancy has to be based mainly on sonographic criteria and not on the clinical status of the mother, such as lower abdominal pain and vaginal bleeding.

First, it is necessary to give the definitions of viable and nonviable pregnancy in order to avoid any confusion. Viable is the pregnancy that is developing normally and the possibility of giving birth to a live baby is high. Nonviable is the pregnancy if it meets at least one of the most commonly accepted criteria that are discussed below and whose possibility of giving birth to an alive infant is zero. Ectopic pregnancy and failed intrauterine pregnancy (IUP) are both nonviable pregnancies. In the middle of these conditions, we meet the "IUP of uncertain viability," the situation where we can visualize a gestation sac in the uterus without the fetal cardiac activity in addition to the absence of definitive findings of pregnancy failure.[3] In this article, we focus on IUPs.

Identifying the Normal Early Pregnancy

Week 4

In the beginning of week 4, the first sonographic signs of the presence of a pregnancy are a thick endometrium and visualization of the corpus luteum cyst, as the depiction of a simple, thick-walled cyst with a "solid" appearance inside the ovary.[4] These are present, because β-hCG that is secreted from the trophoblasts by the first moments of implantation (6th–9th day of conception) allows the corpus luteum to continue the secretion of progesterone. Thereinafter, the endometrium undergoes changes under the constant influence of progesterone: endometrial stroma cells develop into enlarged, round decidual cells.[5] At this stage, if the pregnancy is developing normally, the endometrium has to be thicker than 8 mm. Moschos and Twickler[6] studied the predictive value of endometrium thickness at the outcome of the pregnancy. They concluded that as the endometrial thickness increased, the likelihood of a normal IUP analogically increased: for each millimeter increase in endometrial thickness, the odds for a normal IUP increased by 27%.

The first sonographic evidence of an IUP can be present at 4^{+4}–4^{+6} weeks from the last menstrual period (LMP) as the depiction of the deciduo-placental interface and the exocoelomic cavity (ECC), assessed with transvaginal ultrasound. By this time the size of these structures, measured as a whole, is 2–4 mm. If we perform the scan with a transabdominal probe, these structures can be visualized 1–3 days later, when they reach the size of 10 mm.[2] The decidual formation which later will be part of the placenta and the ECC can be identified as an echogenic trophoblastic ring, composed of the decidua capsularis and the chorion leave as two concentric rings

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surrounding an anechoic gestational sac (if it can be observed). This is the double sac sign.[7] These structures are located within the endometrium and if we want to be more accurate, they are placed in the one side of the midline of the endometrium.

One other very useful sign, helping to identify early IUP and estimating the implantation site is the intradecidual sac sign (IDSS). This sign consists of the threshold level and the discriminatory level. It is seen as an early gestational sac, an intrauterine fluid collection, or an echogenic area in a markedly thickened decidua on the one side of the uterine cavity. This can be better visualized by visualizing the collapsed uterine cavity.[8] Double sac sign and IDSS were very useful in the past, when transvaginal probes were not that widespread and the first scans were performed via the abdominal route. Nowadays, with the increased availability of the transvaginal approach these signs are absent in 35% of the normal early pregnancies.[9]

Week 5

By the first days of week 5, the gestational sac can be first visualized.[10,11] The gestational sac is recognized as a small, thin-walled cystic-fluid collection with rounded edges. At that moment, the gestational sac appears to be empty—there are no visible structures in it. It is located in the central echogenic portion of the uterus, within the decidua. A significant parameter to identify the normal development of the pregnancy is the mean diameter of the gestational sac (MSD). The MSD can be measured as the average of the sagittal, the transverse, and the anteroposterior (AP) diameter of the sac[3] [MSD = (length + height + width)/3]. The transverse diameter is measured as the longest diameter, the AP diameter is the longest diameter perpendicular to the longest diameter, and the transverse diameter is the longest diameter on the transverse section. In normal developing pregnancies, MSD increases 1 mm per day,[12,13] and by the beginning of week 5 it reaches the size of 5 mm. When the MSD reaches the size of 8–10 mm (5^{+3}–5^{+5} weeks), we can visualize the secondary yolk sac (SYS). The SYS is identified as a round structure with a bright outline and a sonolucent center (Figs 1 and 2). The presence of that structure is a strong evidence that the pregnancy is intrauterine.[2]

At this stage of the pregnancy and before the visualization of the yolk sac, we have to be ensured that the depiction of the intrauterine fluid is a real gestational sac of an IUP and not a "pseudosac": the collection of fluid between the two layers of the endometrium that is most commonly seen in ectopic pregnancies.[2] The term "pseudosac" is no longer used in medical practice as the "intrauterine fluid" is now preferred. Besides the intradecidual sign, one other clue helping us define the location of implantation is that the "intrauterine fluid" is located in the center of the uterine cavity, in contrast to the gestational sac that has an eccentric position. In addition, the intrauterine gestational sac appears to be empty and it has a smooth round or oval shape, in contrast to the "intrauterine fluid" that has irregular shape, pointed edges, and it is possible to be filled with debris.[14] Nowadays, the real intrauterine gestational sac can be easily distinguished from the "intrauterine fluid" because of the high availability of high-frequency transvaginal probes in daily medical practice.[2]

Week 6

In the beginning of week 6, we can first have a depiction of the fetal pole inside the ECC as a thickening of the SYS. The fetal pole is placed in the side of ECC that is closer to the uterine wall (Fig. 3). At this moment, the size of the fetal pole reaches 2 mm. This is approximately the time of the very first recognition of the fetal cardiac activity. This is the strongest evidence of a viable pregnancy.[2] The vast majority of authors agree that the fetal cardiac activity should be present when the fetal pole is 2 mm or bigger,[15] since in the 90–95% of normal developing pregnancies the fetal cardiac activity can be confirmed when the size of the embryo is 2–4 mm. Thus, in 5–10% of viable pregnancies this cannot be evaluated, although the pregnancy will continue normally (in a proportion of 5–10% of viable pregnancies, the fetal cardiac activity cannot be confirmed as present when the embryo measures 4 mm).[16,17] In order to avoid false diagnosis of a pregnancy failure, it is recommended to repeat the scan in a week.

During the 6th week as the embryo grows rapidly, we can visualize the amniotic membrane while the amniotic cavity expands. Now, the embryo can be seen away from the SYS, as a separated structure.[2] At this moment, crown rump length (CRL) is 4–9 mm and the size of the gestational sac is 16–40 mm[18] (Fig. 4).

At this point, we believe that it would be extremely helpful to summarize the timeline of the first visualization of the most significant events that occur during early pregnancy: at week 5 the gestational sac first appears, the yolk sac starts to be visible at 5½ weeks and at week 6 we are able to obtain a fetus with a heartbeat.

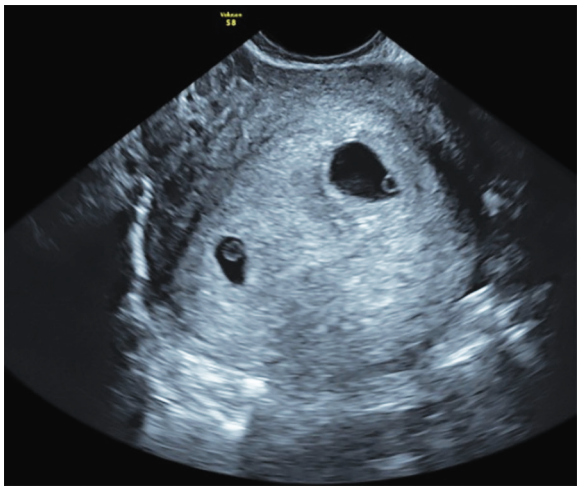


Fig. 1: Twin gestation: Two gestational sacs and two yolk sacs in dichorionic diamniotic pregnancy

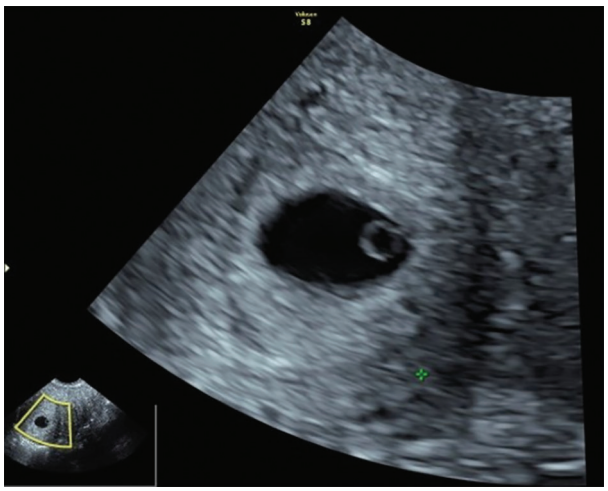


Fig. 2: Gestational sac and secondary yolk sac

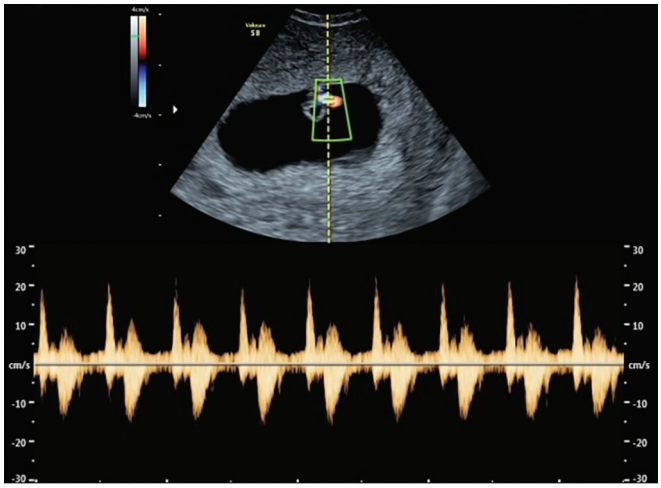


Fig. 3: First visualization of the fetal pole at 6 weeks. Fetal cardiac activity is already present

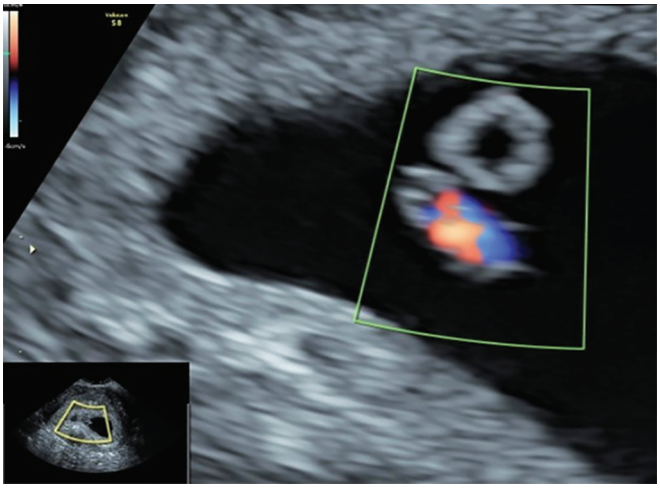


Fig. 4: A 6^{+3}-week gestation: the embryo measures 9 mm and it is away from the yolk sac

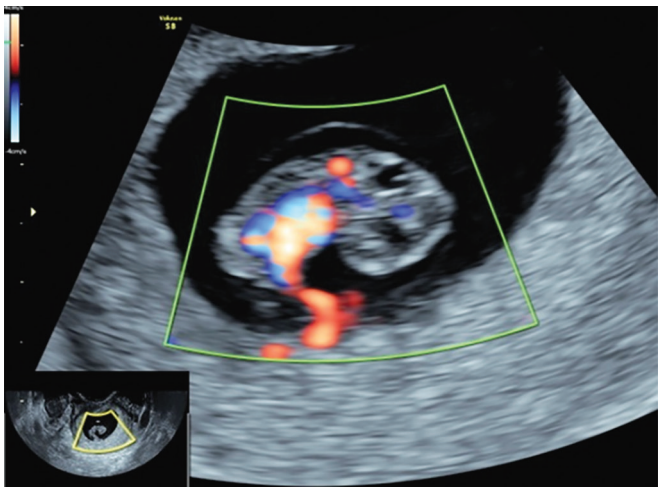


Fig. 5: A 7-week gestation: The fetal head starts to bipolarized and inside it we can first visualize the rhombencephalon, as a sonolucent area

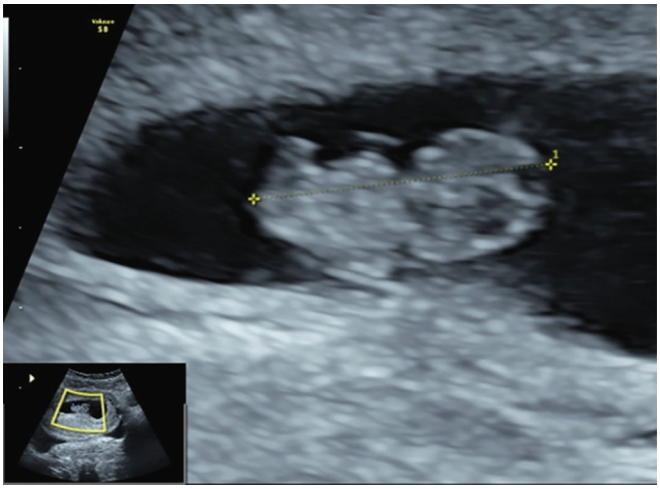


Fig. 6: A 8-week gestation: The embryo measures 18 mm and we can clearly obtain the limb buds. Inside the fetal head we can visualize the developing rhombencephalon

It is important to be aware of the presence of normal deviation of ±½ week.[3,10,11]

Week 7

When the pregnancy reaches 7 weeks, the amniotic membrane and the amniotic cavity continue to expand and become clearer as visible structures. The SYS appears to be suspended in the ECC. At this moment, the fetal pole measures 10–15 mm,[18] and we can clearly obtain fetal head as the embryo starts to polarize (Fig. 5). Inside the fetal head, the first distinct structure that we are able to visualize is the rhombencephalon or hindbrain as a sonolucent area. The rhombencephalon is the primordial forth ventricle and includes the medulla, pons, and cerebellum.[19] Other structures visible in this stage of pregnancy are the umbilical cord and the upper limb buds appearing as small puddles.

Week 8

By the 8th week, the fetal pole measures 16–22 mm. Now the fetal movements are ostensible as the upper and lower limb buds start to be distinct[18] (Fig. 6). At this time, however, the ratio between the fetal parts differs significantly from those in the newborn: the head is big in relation to the whole body and the limbs are quite short.[20] As the week 8 continues, we can see the physiological mid-gut herniation, the fetal stomach,[21] and the vessels of the umbilical cord. The fetal brain starts to acquire distinct structures as the prosencephalon (forebrain), the mesencephalon (midbrain), in addition to the developing rhombencephalon. Figures that may be visible by transvaginal ultrasound are the cerebellum and the choroid plexus.[22]

Week 9

During the 9th week, the fetus and the membranes continue to develop speedily. At this time, the embryo measures 23–30 mm[18] (Fig. 7).

Week 10

As the fetal growth continues, the embryo reaches the size of 31–40 mm. At week 10, we can first be able to have a depiction of the fetal bladder. In addition, by week 10 bone mineralization commences in the clavicle, femur, and in the cranial vault.[23]

Late First Trimester

By the end of week 11 (CRL: 41–52 mm), the fetal stomach has to be visible and by week 12 (CRL: 53–66), the fetal bladder has also to be present. Fetal primitive kidneys starts its function and produces

urine that is passed in the amniotic cavity, causing it to expand.[24] As a result, the amniotic membrane moves toward the fetal plate of the placenta. The ECC and the SYS almost disappear at 12–13 weeks of gestation (Figs 8 to 10).

Diagnosis of Early Pregnancy Failure

As we are getting more familiar with the normal developing pregnancy, we will be able to diagnose an early pregnancy failure more easily. But situations are not always that simple. A false-positive diagnosis of a failed pregnancy is indeed a dramatic condition: if we proceed to medical or surgical intervention in a woman with a pregnancy of uncertain viability without any definitive diagnosis of the failure, we can eliminate or damage a viable pregnancy.[3] In defense of this, the false-negative diagnosis of a failed early pregnancy (a failed pregnancy is diagnosed wrongfully as viable) is so less dramatic, since it can cause only a delay in diagnosis and if the woman is being followed closely, consequences will be eliminated. The first diagnostic criteria for the early pregnancy failure were published in 2011.[25] The major goal of these criteria is to eliminate false-positive diagnosis of a failed pregnancy, with a focus on specificity, which is extremely close to 100%,[3] at the expense of the sensitivity.[26,27]

In this approach, we attempt to present the findings diagnostic—or suspicious—for the early pregnancy failure and they are summarized in Table 1. The cutoff values for every parameter are set in order to eliminate false-positive diagnosis depending on the variety of the experience of the examiner and the normal deviation existing in every different fetus. We believe that it is very important to be mentioned that when findings cannot set the diagnosis as conclusive, the general approach is to repeat the scan in 7–10 days, in order to eliminate any possibility of a mistake.

A clue helping us suspect an early failed pregnancy is limited to developing of MSD: if the MSD does not increase by 1 mm it is a suspicious but not a definite finding of failure of the pregnancy. One other suspicious finding is the depiction of an empty—including neither a yolk sac nor a fetal pole—gestational sac, by the time that MSD measures 16–24 mm. To define the failure as conclusive, the empty gestational sac has to be bigger than 25 mm.[3]

This cutoff value was established because recent studies concluded that the possibility of false-positive diagnosis (specificity) of a failed pregnancy is 100% when the MSD is 21 mm without the visualization of a fetal tissue.[28] Interobserver variation in the measurement of MSD is calculated as ±19%.[3] Mathematically, 25 mm is the upper limit of the depiction of an empty gestational sac in order to set the diagnosis of a failed pregnancy as definite.

A definitive diagnosis of an early pregnancy failure can be made at 6 weeks when the crown-rump length is larger than 7 mm and the cardiac activity is absent. We suspect a failure of the pregnancy when the crown-rump length is less than 7 mm and the fetal cardiac activity is not present and when the embryo is absent 6 weeks from the LMP. One other suspicious finding regarding the failure is a small gestational sac in relation to the size of the embryo: the difference of the size of MSD and the crown-rump length is less than 5 mm. "Soft markers"[2] that may be present at a failed IUP are a yolk sac bigger than 7 mm and an empty amnion, visualized to be adjacent to the yolk sac.[3]

As the pattern above, the cutoff value of a CRL larger than 7 mm and absence of the fetal cardiac activity are confirmed as the upper limit to set the definite diagnosis of an early pregnancy failure,

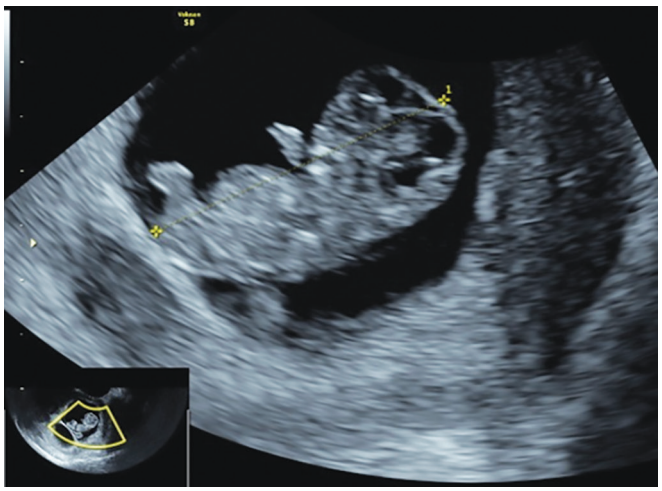
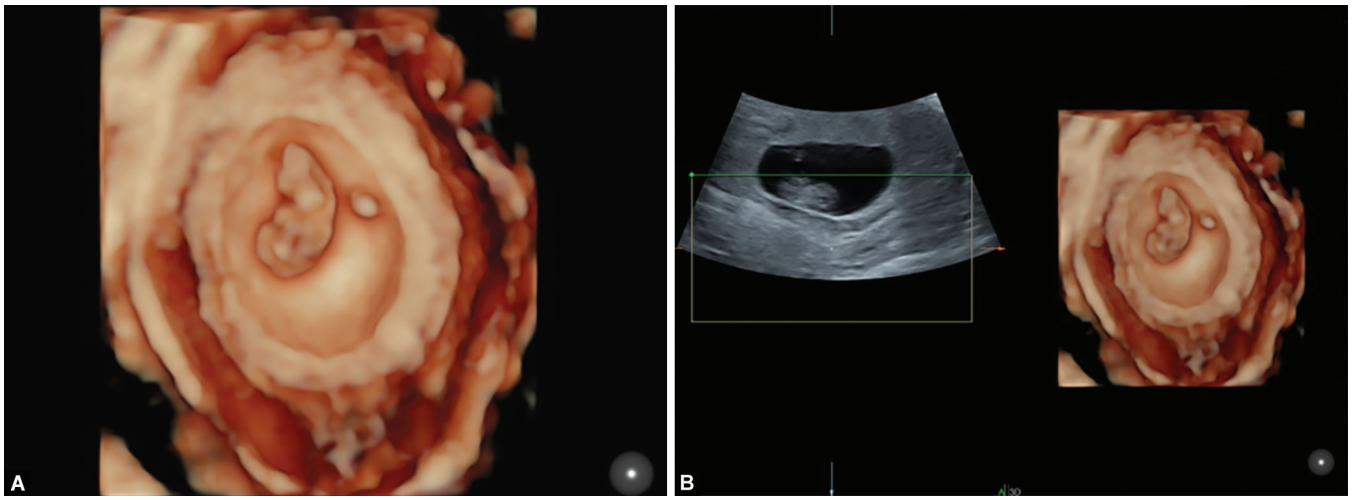


Fig. 7: A 9-week gestation: The embryo measures 28 mm. Inside the fetal head we can visualize the prosencephalon, mesencephalon, and rhombencephalon



Figs 8A and B: (A) A 7-week gestation: The embryo measures 15 mm viewed with 3D imaging. The fetal shape is visible, as it is the yolk sac; (B) 3D imaging of a 7-week fetus

because a study that included 2,845 women had concluded that specificity of a failed pregnancy is 100% when the CRL is 6.2 mm[28] and the fetal cardiac activity is absent. If we add the interobserver variation in the measurement of CRL, which is ±15%, the final number is 6.9 mm.[3]

The presence of a yolk sac is a remarkable clue for the diagnosis of an early failed pregnancy. If we obtain a yolk sac without evidence of the fetal cardiac activity, we can set the diagnosis of the failure as definite when the fetal cardiac activity is still absent in a repeat scan in 11 days. The diagnosis will be possible, but not definitive, when the time between the scans is 7–10 days. When the yolk sac cannot be visualized, the timeline needed for setting the diagnosis is different: the pregnancy is definitely nonviable if the fetal cardiac activity is absent if the repeat scan is performed in 2 weeks and possible when the repeat scan is performed 7–13 days later. Bourne and Bottomley[25] highlighted the fact that measurements of serum hCG and progesterone have no role in the management of a suspected diagnosis of an early failed pregnancy.

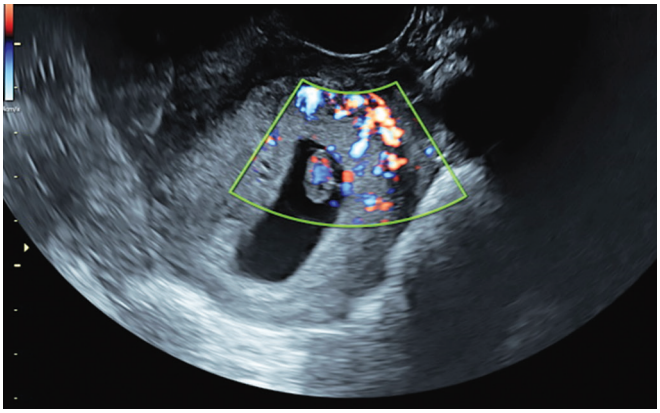


Fig. 9: Normal blood supply of the placenta and the fetus at 7 weeks of pregnancy. That was a viable pregnancy that carried on without complications

Even when the fetal cardiac activity is present, concerns are not completely faded. The FHR is increasing in early pregnancy: by week 6, the fetal cardiac mean rate is about 110 beats per minute (bpm) and by week 7 the fetal cardiac activity is faster than 140 bpm.[29] The FHR is a parameter whose prognostic predictive value has been doubted over the years. Bourne and Condous[2] noticed that evaluation of FHR has limited prognostic predictive value and it should be only evaluated for research. Some studies carried out some years before concluded that slow fetal cardiac activity has been associated with spontaneous pregnancy loss.[29–32] A meta-analysis that occurred in 2017, whose aim was to summarize the sonographic factors that could predict more accurately a miscarriage,[33] claimed that fetal bradycardia has the highest sensitivity [68.41% (95% CI 43.62–85.84%)] and specificity [97.84% (95% CI 94.50–99.17%)] for prediction of miscarriage with the cutoff value placed on 110 bpm. Other interesting findings were that sensitivity increased significantly (from 68.41% to 84.18%) in women with a threatened miscarriage [sensitivity: (95% CI 42.02–97.50%), specificity: 95.68% (95% CI 87.76–98.56%)] and that studies occurred after the year 2000 have significantly higher sensitivity than studies performed before 2000. Data from different studies are present in Table 2. Authors agreed that when fetal bradycardia is present in early pregnancy, a repeat scan

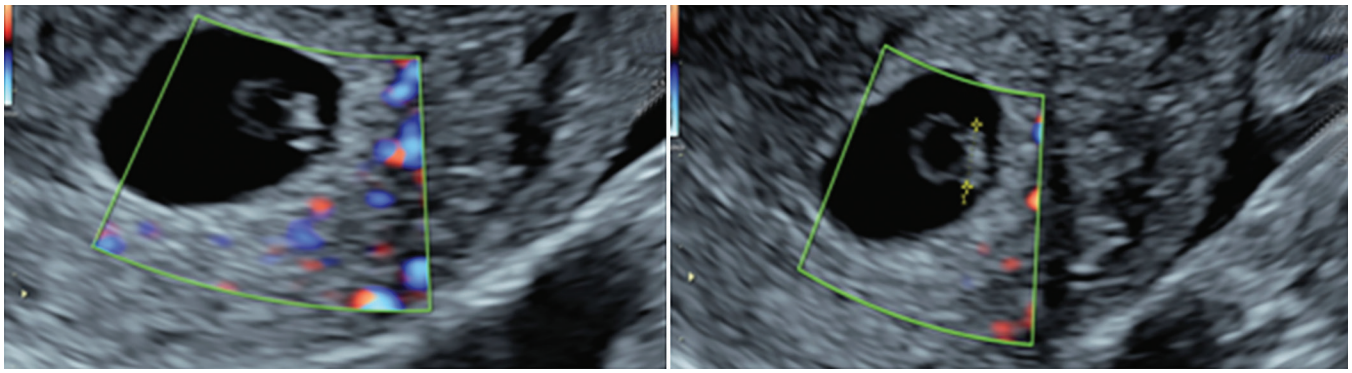


Fig. 10: Poor vascularization of a 6-week fetus. The CRL is 3.5 mm and the heart rate is just visible. The vascularization of the fetus and the placental area is poor. This pregnancy ended up as a missed miscarriage

Table 1: Diagnostic and suspicious findings of pregnancy failure (modified from Dubilet and Benson, 2013[3])

Findings diagnostic of pregnancy failure	*Findings suspicious of pregnancy failure*
MSD ≥25 mm and absence of fetal tissues	MSD not increasing 1 mm per day
	MSD 16–24 mm and absence of fetal tissues
CRL ≥7 mm and absent fetal cardiac activity	CRL <7 mm and absent fetal cardiac activity
	Absence of embryo 6 weeks after last menstrual period
	Enlarged yolk sac (>7 mm)
	Small gestational sac in relation to the size of the embryo (MSD and CRL differ <5 mm)
Absence of embryo with heartbeat ≥2 weeks after a scan that showed a gestational sac without a yolk sac	Absence of embryo with heartbeat 7–13 days after a scan that showed a gestational sac without a yolk sac
Absence of embryo with heartbeat ≥11 days after a scan that showed a gestational sac with a yolk sac	Absence of embryo with heartbeat 7–10 days after a scan that showed a gestational sac with a yolk sac
	Empty amnion

Table 2: Fetal heart rate cutoff value (bpm) and specificity in different studies throughout the years

Authors	*FHR cutoff value (bpm)*	*Specificity (%)*
Laboda (1989)	90	100
Machiers (1991)	100	98
Benson and Doubilet (1997)	80	100
Stefos (1998)	85	100
Chittacharoen (2004)	120	95
Bourne and Condous (2007)	–	Limited value
Dede (2010)	130	85
Maged and Mostafa (2013)	110	99

in a week is necessary for evaluating the viability of the pregnancy, before any intervention.[33,34]

It would be an omission if we do not mention SCHs and their predicting value in early pregnancy. A SCH can be obtained as a crescent-shaped anechoic area between the chorionic membrane and the endometrium.[34] When a SCH is present, the overall possibility of the pregnancy to fail is about 9%. Different studies find this percentage from 8.9% to 17.6%.[35–38] The factors increasing the possibility of the failure are the size of the hematoma and maternal and gestational age: if a hematoma is diagnosed at or before 7 weeks the demise rate is about 19.6%, in contrast to the possibility of failure if the diagnosis was established later than 8 weeks which is 3.6%. If the diagnosis was made between 7th week and 8th week, the demise rate is 14.6% ($p < 0.001$).[37] The factor that is statistically more significant is the hematoma's size and more specifically the characterization of the hematoma's size as the estimated fraction of the gestational sac size: demise rate is 5.8% if the SCH was 10% of the sac size or less and 23.3% when the SCH size was greater than 50% of the sac size ($p < 0.001$). Last but not least, if the mother is older than 35 years, the possibility of failure is higher (demise rate: 19.6%) than mothers younger than 35 years (demise rate: 9.6%, $p = 0.007$). Interestingly, the presence of vaginal bleeding has no predictive value in the outcome of an early pregnancy ($p = 0.84$). The site of hematoma is also important and should be mentioned.

Early Pregnancy Blood Supply Assessment and Safety of Ultrasound

Intervillous circulation, which is established during the early weeks of first trimester, is a process that starts with trophoblastic invasion of the deciduas, with the release of proteolytic enzymes, which facilitate the penetration and erosion of the adjacent maternal capillaries, with formation of the lacunae and then the trophoblast invades deeper portions of the endometrium up to the spiral arteries.[39,40] This gradual process finishes with direct opening of the spiral arteries in the intervillous space under the fully developed placenta. There is no doubt that studies of maternal-fetal circulation in early pregnancy may help for better understanding of physiological and pathophysiological hemodynamic changes. Investigation of maternal (main uterine, arcuate, radial, and spiral) arteries, placental (umbilical, chorionic arterioles) vessels, and fetal (aorta and intracranial circulation) arteries flow patterns may help in order to diagnose abnormal implantation.[41–47] Uteroplacental blood flow may be different in missed abortions and nonembryonic gestational sacs than in normal pregnancies. Women with missed abortions and nonembryonic gestational sacs frequently showed a facilitated uteroplacental blood flow, as indicated by a higher number of myometrial blood vessels, higher frequency of flow in the intervillous space, and lower vascular impedance, compared with those in normal pregnancies.[48] The indices of impedance to flow decreased with gestation and there was a progressive fall in these indices from the uterine artery, through the radial, to the spiral artery. Blood velocity in the uterine artery increased exponentially with gestation. The significance of transvaginal color and pulse wave Doppler in the diagnosis of pathologic early intrauterine and tubal pregnancy was assessed trophoblastic vessels could not be detected. These findings suggest ineffective early placentation in pathologic pregnancies.[44–46]

Diagnostic ultrasound has been used for many years with a remarkable history of safety during the standard clinical practice. Intense ultrasound could damage the embryonic tissue. Teratogenicity has been reported in animal fetuses exposed to high temperature. Since the main biological effect of ultrasound absorption in tissue is an increase of temperature (thermal effect), users of diagnostic ultrasound should be familiar with the ultrasonic intensity of their machines and with methods to prevent thermal hazards to the embryo.[41] On the screen of all modern machines, the thermal index (TI) of any scanning activity is continuously displayed. TI 1 stands for 1°C temperature elevation above 37°C and, for example, TI 3 means a temperature rise of 3° from 37°C to 40°C in the tissue. The difference between ultrasonic physiotherapy and diagnostic Doppler ultrasound is only the duration of exposure, whereas both operate with maximum intensities of 1–3 W/cm^2. Temperature increases not only in the sample volume but also in all tissue layers passed on the way. These values should be taken into account when assessing early pregnancies.

Conclusion

It is commonly accepted that the failure of a desirable pregnancy is a dramatic incident. In order to eliminate the possibility of a wrong diagnosis and to put into practice the Hippocratic "Do no harm," the definitive diagnosis of a failed early pregnancy has to be set by the above-said guidelines strictly. If there are any doubts about the failure of the pregnancy, a repeat scan in 7–10 days is necessary for saving both the mother and the obstetrician from unpleasant feelings and situations.[48]

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