

Diagnostic Methods of Ectopic Pregnancy and Early Pregnancy Loss: a Review of the Literature

Diagnostische Methoden bei Frühabort und Extrauterin gravidität: eine Übersichtsarbeit

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Key words

- early pregnancy loss
- fetal demise
- ectopic pregnancy
- β -hCG
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Schlüsselwörter

- Frühabort
- Fruchttod
- Extrauterin gravidität
- β -hCG
- Ultraschall

Abstract

This review article presents recent evidence on early pregnancy loss and ectopic pregnancy. In the light of recent evidence, the β -hCG discriminatory zone may be extended in clinically stable cases without evidence of bleeding. A possible cut-off is 4300 mIU/ml, which corresponds to when a sonographer should detect an intrauterine pregnancy. Embryonic demise can be confirmed when a transvaginal ultrasound finding shows no heartbeat in an embryo of more than 7 mm CRL, no embryo in a gestational sac having a mean sac diameter of more than 25 mm, or no appearance of an embryo within 7–10 days after the primary examination. These are considered definitive signs of embryonic demise. Suggestive signs of embryonic demise require closer monitoring of the pregnancy.

Zusammenfassung

Der vorliegende Übersichtsartikel gibt einen Überblick über die neuesten Forschungsergebnisse zu Frühabort und Extrauterin gravidität. Nach den neuesten Forschungsergebnissen könnte der Referenzbereich für β -hCG-Werte in klinisch stabilen Patientinnen ohne Blutungen ausgedehnt werden. Als möglicher Cut-off-Wert wird ein Wert von 4300 mIU/ml diskutiert, welcher ungefähr dem Zeitpunkt entspricht, an dem die Schwangerschaft auch per Ultraschall festzustellen sein sollte. Ultraschall kann zur Bestätigung eines Frühaborts dienen, wenn sich bei einem Embryo mit einer SSL von mehr als 7 mm keine Herzaktivität feststellen lässt, bzw. sich kein Embryo in einer Fruchtblase mit einem durchschnittlichen Durchmesser von mehr als 25 mm befindet, oder wenn kein Embryo innerhalb von 7–10 Tagen nach der Erstuntersuchung aufzufinden ist. Diese Befunde sind allesamt als definitive Hinweise auf einen embryonalen Tod zu werten. Bei Anzeichen, die auf einen Frühabort hindeuten, ist eine engmaschige Überwachung der Patientin notwendig.

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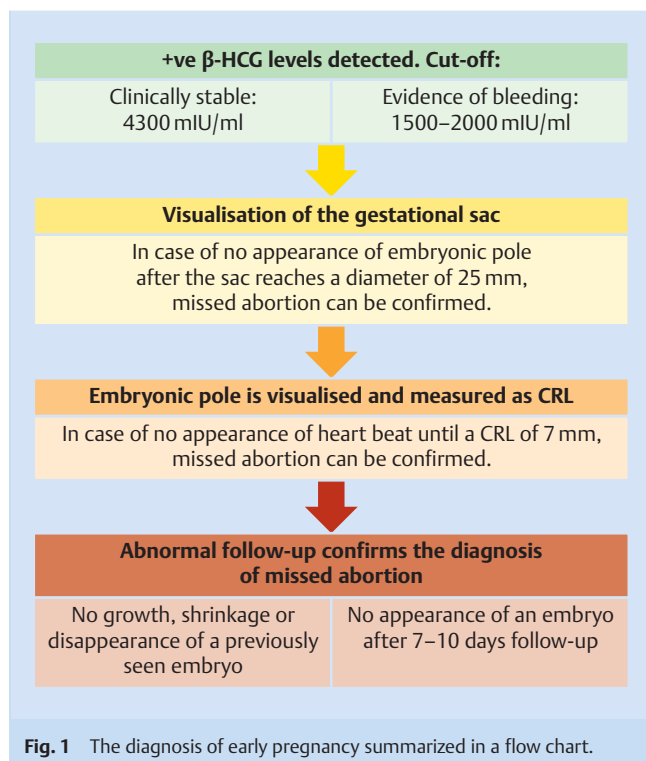
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Abbreviations

β -hCG	β subunit of human chorionic gonadotrophin
CRL	Crown rump length
CDC	Centers for Disease Control and Prevention
i. m.	Intramuscular
i. v.	Intravenous
MSD	Mean sac diameter

Introduction

The primary target of an effective and efficient prenatal care system is to differentiate low from high risk pregnancies. A low risk pregnancy reflects a physiological course of gestational events, which requires distant monitoring for any abnormalities that would detect an abnormality that allows for reclassification of the gestation. Conversely, a high risk pregnancy requires a closer follow-up performed in specialized prenatal care facilities, thus reducing the probability of perinatal morbidity and mortality [1–3]. Two of the primary targets of prenatal surveillance is diagnosing abnormalities such as ectopic pregnancies, and detecting early pregnancy loss.



An important and possibly lethal abnormality is ectopic pregnancy. It is crucial to acquire medical skills and knowledge to differentiate early between an intrauterine and an ectopic pregnancy. The incidence of ectopic pregnancies in cases presented to the gynecology emergency department due to first trimester bleeding and/or pain ranges from 6 to 16%. According to the Centers for Disease Control and Prevention (CDC), the absolute number of hospitalizations due to ectopic pregnancy rose in the USA from 17 800 cases in 1980 to 88 400 in 1989 [4]. Due to the increasing incidence of tubal pathology, secondary to pelvic inflammatory diseases, the overall occurrence of ectopic pregnancy is also increasing [5]. According to the national data collected by the CDC, the overall occurrence of ectopic pregnancies is approximately 20 over 1000 pregnancies [4]. In a case series of 147 patients with ectopic pregnancies, 99% noted abdominal pain; 74% had a history of amenorrhea; 56% reported vaginal bleeding, and 78% experienced a rupture [6]. Currently, the gold standard of diagnosis for first trimester bleeding and/or pain is measuring β -hCG levels above the discriminatory zone (1500–2000 mIU/ml) without sonographic evidence of an intrauterine pregnancy [7]. Suspecting an ectopic pregnancy is an indication for patient hospital admission. The treatment of an ectopic pregnancy can include expectant management, medical management (i. m. or i. v. application of methotrexate) or a surgical procedure. As will be discussed later, taking an upper limit of 2000 mIU/ml to confirm the diagnosis of an ectopic pregnancy will miss 33% of normal intrauterine pregnancies, making the decision to terminate a pregnancy in clinically stable cases a challenging decision [8]. Another strenuous decision in some instance is the diagnosis of early pregnancy loss, also known as spontaneous abortion. Spontaneous abortion is sub-classified as missed, incomplete, and complete abortion, and it is the most common complication during early gestation [9]. With advancing gestational age, the incidence of spontaneous abortion decreases. The majority of the

abortions occur before the 12th week of gestation, whereas after the 15th week, the overall risk for spontaneous abortion is approximately 0.6% [10]. According to an embryoscopic and cytogenetic analysis of 233 missed abortions during the first trimester, 75% of the cases had an abnormal karyotype, 18% had a normal karyotype with a morphological defect, and 7% of cases had no embryonic or chromosomal abnormality. In this study, missed abortions were examined using a hysteroscope for morphological analyses, and an additional fetal or embryonic karyotype was done to complete the diagnosis [11]. More recent research shows that the current cut-offs of the mean gestational sac at which no embryo is seen, and crown-to-rump (CRL) lengths at which no heartbeat is seen, lead to the misdiagnosis of healthy pregnancies [12].

In some instances, the diagnosis is a visual diagnosis, e.g. in cases when the embryo showed a positive heartbeat that later ceased to persist, while in other cases the situation can be much more difficult, for example where the mean sac diameter is 23 mm without an evident embryo. In such an unclear clinical scenario, the obstetrician or sonographer is left with a dilemma of informing the patient about a poor, good, or undefined gestational prognosis. Thus, the diagnostic spectrum ranges between extremes. To avoid diagnostic errors with fatal consequences, extensive knowledge about the embryonic development in early pregnancy is crucial. Therefore, this review summarizes the available data relating to the impact of amenorrhea, β -hCG-levels, and sonographic signs for the diagnosis of early pregnancy.

Significance of Amenorrhea

Amenorrhea is the absence or abnormal cessation of the menses. It is sub-classified into primary and secondary amenorrhea according to the time of occurrence. Primary amenorrhea is defined as the absence of menses by the age of 15 in the presence of secondary sexual characters and normal growth. This is also known as the absence of menarche [13]. Secondary amenorrhea is defined as the absence of menses for more than three cycles or six months in women who previously had menses. The most common cause of secondary amenorrhea is pregnancy, making it a cardinal sign of pregnancy. Lactation, pregnancy, and menopause cause secondary amenorrhea in 96–97% of cases. The remaining 3–4% are due to pathological causes [14, 15]. It is therefore important to rule out pregnancy in cases of secondary amenorrhea, even if a patient reports having sexual intercourse during a safe period, under hormonal or barrier contraception. Confirming or ruling out a pregnancy is most reliably done by determining or detecting β -hCG in maternal serum or urine.

Positive β -hCG in the Urine and/or Serum

β -hCG is secreted by the conceptus in the maternal circulation after implantation. After fertilization, between the 8th and 10th day post ovulation, the conceptus migrates towards the uterine cavity, usually implanting itself by an aggressive burrowing under the endometrium, and β -hCG is secreted into the maternal circulation. Subsequently, the β -subunit of β -hCG is detectable in the maternal serum and in the urine using immunoassay techniques [16, 17]. There are different commercially available assays, having different standards. Therefore, it is important, if a follow-up is done, to use the same immunoassay.

β -hCG can be detected as early as six days after presumed conception and peaks between 56 and 68 days, with a nadir at 18 weeks. In a normal, intrauterine pregnancy, during the first 30 days after implantation, the β -hCG measured doubles every 29 to 53 hours. An ectopic or unhealthy pregnancy shows a slower rise or even decline of the level in maternal serum [18–20] and no secondary rise of β -hCG levels can be seen [21]. Based on this, measurement of the β -hCG can indirectly give a hint of the vitality of the pregnancy.

β -hCG can be detected in the serum long before the pregnancy is visible using ultrasound techniques. Many studies were conducted to determine the minimum and maximum levels by which an embryo has to be seen. The serum level of β -hCG above which a gestational sac should be visualized is called the discriminatory zone for β -hCG [22], which is considered to be between 1500 to 2000 mIU/ml [23]. This level is obviously higher (6500 IU/L) using transabdominal ultrasound. In earlier publications thresholds of 1000, 1500, and 2000 mIU/ml were published, which might seem contradictory [23, 24].

Due to some confounding variables, β -hCG levels may be elevated above expected, thus crossing the 2000 mIU/ml level without any sonographic evidence of gestation.

While measuring β -hCG alone can be an indirect test to assess the vitality of the pregnancy, a combination with sonographic examination can improve the accuracy of this method. The variations in resolution, transducer frequencies, manufacturers of ultrasound scanners and sonographers play a significant role in the detection of small gestational sacs [8, 27].

The German guidelines, AWMF, state that a chorionic sac should be detected starting from a β -hCG level of 1500 mIU/ml. A cut-off after which the absence of an intrauterine pregnancy should be suspected is not given [55].

There are conflicting opinions about the upper limit of the discriminatory zone using β -hCG when combining it with transvaginal ultrasound. Recent trials tend to lift the upper limit of the discriminatory zone in order to avoid erroneously destroying healthy pregnancies [27]. Mehta et al. analyzed 676 pregnancies and showed that taking a cut-off of 2000 mIU/ml would miss one third of the intrauterine pregnancies [8]. In another study, Doubilet et al. examined 202 cases, where transvaginal ultrasonography showed no intrauterine evidence of pregnancy with a positive β -hCG test on the same day; 4.5% of the cases showed a β -hCG of above 2000 mIU/mL. In this series, none of the cases were diagnosed with extrauterine gestation. The highest value that preceded a live-born term baby was 4336 mIU/mL. In this cohort, 13.8% of cases had an “uncertain” first trimester outcome, 77.2% were vital pregnancies by the end of the first trimester, and 9% had spontaneous first-trimester pregnancy loss; 66.8% of all the gestations were live born. The authors concluded that in cases when sonographic findings are inconclusive, the β -hCG discriminatory level should not be used to determine the management of a hemodynamically stable patient with suspected ectopic pregnancy [27].

Sonographic Evaluation of an Intrauterine Early Pregnancy

Prerequisites for establishing a proper diagnosis

A technically adequate exam, using high resolution transvaginal ultrasound devices performed by an experienced sonographer, is the basic requirement for a proper diagnosis.

As the uterus is inside the bony pelvis, the best visualization is achieved by transvaginal sonography. As the pregnancy continues and the uterus rises outside the pelvis, transabdominal sonography becomes the method of choice [28].

Physiological sonographic findings in early embryonic development

Basically, the sonographic structures appear in sequence. The first sonographic sign is the gestational sac, which is usually visible at 4.5 to 5 weeks of gestation. It is characterized by an echolucent sac surrounded by two concentric echogenic rims, also called double sac sign, appearing at 5.5 to 6 weeks [29]. This sac is usually round in shape and the echogenic rim represents the chorionic cavity. The intradecidual sign describes a fluid collection inside an echogenic rim located within a markedly thickened decidua on the lateral aspect of the uterine cavity [30]. Once this gestational sac is detected in an intrauterine location, an intrauterine pregnancy is diagnosed. Except for rare cases of heterotopic pregnancies, a normal course of events is expected [31]. Since the sac grows by approximately 1 mm/d, measuring the sac can be used to date the pregnancy. Therefore, calipers should be placed inside the sac, not including the echogenic rim. Most modern ultrasound devices can calculate the gestational age based on the sac diameter. Measuring the mean sac diameter (MSD) is done by calculating the mean of three orthogonal sac diameter measurements. However, with progressive pregnancy, this procedure is less accurate.

The next structure that appears during the embryonic development is the yolk sac. It can be detected at the start of the 5th gestational week confirming an intrauterine healthy pregnancy. Morphologically, it is described as a round structure with echolucent center and echogenic periphery [32]. The yolk sac reaches a maximal diameter of 6 mm at the age of 10 weeks [33], then it migrates to the periphery of the sac and disappears [34]. Thereafter, the embryo appears, which has also been designated as the embryonic pole or embryonic disc [35].

With ongoing pregnancy, the CRL can be measured. It is the standard biometric measurement of the embryo in the first trimester, defined as the longest straight line from the cephalic to caudal (rump) end of the embryo [36]. It can determine the gestational age with an accuracy of plus/minus three days [37, 38]. Within this embryo, the embryonic heartbeat appears between 5.5 and 6 weeks of gestation, after which the risk of an abortion is reduced. However, after the 15th week of pregnancy, the accuracy of the CRL is reduced to within ± 8.4 days [40]. Between the 11 + 0 and 13 + 6 weeks of pregnancy, the nuchal translucency can be measured and correlated with patient and biochemical data to calculate the risk for trisomy 13, 18 and 21 [39].

Pathological sonographic findings in early embryonic development

Despite technical advances and sonographer training, human errors and physiological variations can result in over- and underestimation of the gestational age, which may lead to misdiagnosis. Different equations are used to curtail errors, yet cannot eliminate them [41, 42]. Extensive research has been conducted to reduce errors and avoid the misdiagnosing an early pregnancy loss. Therefore, signs of fetal demise have been subdivided into definitive and suggestive signs.

Definitive signs are indicators of a missed abortion, and the presence of one of the signs is enough for such a diagnosis. Each definitive sign and its reasoning is described below [12] (● Fig. 1):

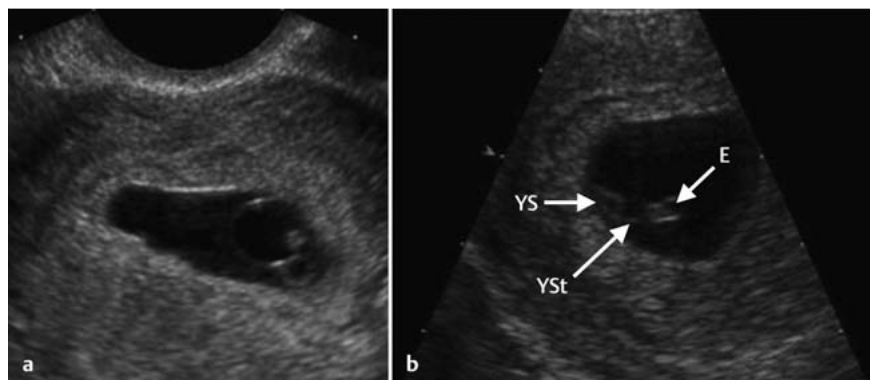


Fig. 2a and b **a** Expanded amnion sign: transvaginal US of a small embryo surrounded by an amniotic sac. This sac is too big for the measured CRL. For early embryos, the CRL is proportionally related to the amnion diameter. This embryo should be approximately 10 mm in size, much larger than in this case (published with permission) [46]. **b** Yolk stalk: an embryo (E) of a CRL < 5 mm and no cardiac activity. Although short, a yolk stalk (YST) can be recognized separating the embryo from the yolk sac (YS), which indicates a more advanced gestational age than would have been concluded from the CRL alone (published with permission) [49].

- ▶ No embryo in the gestational sac with mean sac diameter of more than 25 mm.

The previous cut-off for the gestational sac diameter used for case of an empty sac, using transvaginal ultrasound, was 16 and 20 mm. Setting the cut-off at 16 mm will have a 4.4% false positive rate, i.e. 4.4% will be pregnancies falsely terminated, while setting a cut-off at 20 mm will give a 0.5% false positive rate [12]. One study found an 18.78% interobserver variation when measuring a mean sac diameter of 20 mm with an interobserver variation span from 16.8 to 24.5 mm. Taking this observation into account, the cut-off of the gestational sac diameter could be extended to 25 mm to reduce the false positive rate to 0.5% [12].

- ▶ No heart beat in an embryo of more than 7 mm CRL.

In current practice, a pregnancy is labeled as a missed abortion if an embryo reaches a CRL of 5–6 mm with no evidence of heartbeat. The German guidelines mention that a heartbeat should be seen starting from a mean sac diameter of 20 mm (55). When measuring a CRL of 5 mm, there was an inter-observer variation from 4.1 to 5.9 mm. A CRL of 6 mm had an inter-observer variation of 5.4 to 6.7 mm. It is therefore recommended to extend the CRL at which a heartbeat should be seen to 7 mm.

- ▶ No growth, shrinkage or disappearance of a previously seen embryo.
- ▶ No appearance of an embryo after 7–10 days follow-up.

In contrast to the definitive signs, the suggestive signs of fetal demise have not proven to be as powerful in the prediction of embryonic demise as definitive signs in larger studies. Thus, these signs are taken as warning signs of possible miscarriage and indicate the need for serial sonographic monitoring. The more suggestive signs found in a pregnancy, the worse the prognosis. Below is an explanation of the suggestive signs:

Embryonic bradycardia

As mentioned before, the embryonic heartbeat should be seen using transvaginal ultrasound by 6 weeks post-menstrualis. Thereby, the embryonic heart rate increases between 5.5 to 10 weeks from 100 to 150–140 beats per minute. Embryonic bradycardia between 6 to 8 weeks of gestation, defined as less than 110 beats per minute, is suggestive of a poor prognosis. Again, a sonographic follow up is recommended within three to four weeks [43].

First trimester oligohydramnios, small gestational sac

Sonomorphologically, a small sac is relative to the size of the embryo being observed. The quantitative method to estimate a small gestational sac is by subtracting the CRL in mm from the mean sac diameter in mm. If it is less than 5 mm, subsequent demise

can be predicted in 94% of cases [44]. Although often having a poor outcome, studies have shown a 35% survival rate, making it only a suggestive sign and not a definitive sign for termination [45].

The expanded amnion sign

This sign can be detected sonographically since a relation is observed between the amniotic sac and the embryo. Normally the amnion grows in direct linear proportion to the CRL. Seeing the amniotic cavity indirectly implies the presence of an embryo with a positive heartbeat. An absence of a heartbeat suggests embryonic demise, yet the sign by which the termination of pregnancy is recommended must be the absence of a heartbeat in an embryo with a CRL of more than 7 mm. Other amniotic abnormalities with poor embryonic outcomes are amniotic cavities with a wavy outline and a thick amnion that approaches the yolk sac thickness [46, 47] (● Fig. 2).

Embryonic growth rate

A growth rate of less than 0.673 mm a day used to be a cut-off for suspecting a miscarriage. This observation was reported to have a specificity of 90.1% and a sensitivity of 61.7% for diagnosing miscarriage. Reports suggest using a cut-off ≤ 0.2 mm per day to predict a miscarriage to minimize the false positive diagnosis to zero [48]. In contrast, clinical practice takes into account that a slow or even absent growth rate of the gestational sac is not necessarily associated with miscarriage. The new cut-off value for CRL growth of 0.2 mm a day is always linked with embryonic demise. Yet, it is not recommended to use the growth rate abnormalities of the gestational sac alone as a marker of fetal demise [48].

Yolk sac abnormalities

Yolk sac abnormalities affect the size (size more than 6 mm), the number (more than one per embryo), the shape (irregular) or the echogenicity (solid or calcified). In the literature, a yolk stalk sign was described. This sign occurs when an embryo, smaller than 5 mm, is identified without a visible heartbeat yet the embryo is not immediately adjacent to the yolk sac. In healthy pregnancies, the yolk stalk does not exist in the early phases. In contrast, the mentioned sign was observed in pregnancies that ended in fetal demise [49].

Presence of blood in the uterine cavity

Blood seen sonographically as echogenic debris or a fluid level in the uterine cavity is also a negative predictor. A chorionic bump is an uncommon finding during pregnancy that may be a hematoma bulging into the gestational sac or a resorbing twin. This



Fig. 3 Retrochorial hematoma in the first trimester on lining the anterior wall of the uterus (marked by multiple white squares in the image – image provided by the authors).

should draw the attention of obstetricians to closely follow up the pregnancy [50]. It was also reported that subchorionic bleeding may correlate with embryonic demise. However, this is not clear cut [51] (● Fig. 3).

Low implantation site of the embryo or gestational sac

A low implantation position may indicate an abortion in progress. This is detected sonographically by caudal movement of the sac and clinically by vaginal bleeding and dilatation of the cervix. In addition, it may also indicate cervical ectopic pregnancy, which is associated with a negative maternal and embryonic outcome, a nabothian cyst, or a normal sac with a uterine contraction [52].

Heterotopic pregnancy

Finally, a pregnancy being intact and intrauterine does not exclude a concurrent extrauterine pregnancy. This is termed as an heterotopic pregnancy. The incidence of heterotopic pregnancy ranges between 1/3889 to 1/30000 in the general population, yet shows an incidence of 1/100 in pregnancies following in vitro fertilization with embryo transfer [53,54]. Due to the presence of intrauterine gestation, the diagnosis of a heterotopic pregnancy remains challenging. The extrauterine pregnancy may be located in the fallopian tube, cervix, caesarean section scar. The latter one is expected to increase alongside with the increasing rate of caesarean sections [56,57].

Conclusion

Based on the retrospective studies reviewed, the diagnosis of early pregnancy loss and ectopic pregnancy could be made more accurate with a reduction in unnecessary terminations of physiological gestations. The new extensions of β -HCG, definitive and suggestive signs could therefore reassure the physician in offering a more confident diagnosis for the patient.

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Conflict of Interest

None.

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