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Predictive factors of early pregnancy failure. A literature review

Abstract

Embryonic demise is the most common event in the lives of women during theirs reproductive time with a rate of about 25%. The aim of this review is to outline the most important paraclinic and biological prognostic parameters. English language articles containing keywords like "embryonic demise", "predictive factors" which were searched using Medline and Pubmed. Systematic reviews, retrospective and prospective studies, clinical trials focused on this subject were selected. Informative value of the references of selected articles was used as base for further relevant headlines. Among the most significant reported predictive factors are the distance between the yolk sac (YS) and embryo, also known as the yalk stalk sign, the progesterone and β human chorionic gonadotropine levels. Low levels of biomarkers and abnormal appearance of gestational sac, crown-rump length and YS are considered worst prognostic factors and may lead to a poor outcome.

Keywords: *embryonic demise, predictive factors, yolk sac, gestational sac*

Carmen Elena Bucuri[1,2], Andrei Mihai Malutan[1,2], Razvan Ciortea[1,2], Renata Lacramioara Nicula[1,2], Carina Mihu[2], Mihnea Istrate[2], Dan Mihu[1,2]

1. Dominic Stanca Clinic
2. "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Correspondence:
Dr. Nicula Renata Lacramioara
e-mail: bucuri.carmen@umfcluj.ro

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Introduction

One in four pregnant women will miscarry at some time during reproductive life, knowing that the incidence of early embryonic demise is higher compared with other early pregnancy complications[(1)]. Successful blastocyst implantation requires precise synchronization between the embryo and the uterine environment. The endometrium is a specialized and hormonal dependent tissue, which does not allow embryos to adhere throughout the menstrual cycle[(2)].

Harmful effect on the tissues, especially on the trophoblastic tissue, occurs due to abnormally high concentrations and high oxygen fluctuations. There is increasing evidence which indicates that failure of placentation is associated with an imbalance in reactive oxygen species which will further affect placental development and function and may subsequently have an influence on both the fetus and the mother[(3)]. These data suggest that embryonic growth is highly sensitive to disruption by reactive oxygen species, and maintaining a low oxygen environment inside the human uterus during early pregnancy, may confer protection[(4)]. Recent data shows an association between intrauterine oxygen concentration in vivo and specific placental proteins[(5)].

Ultrasound examination is the elective method in the diagnosis of early embryonic demise[(1)]. Transvaginal sonography (TSV) provides accurate images of the early gestational sac and has also been proven to confer important clues to the epidemiology and pathophysiology of early pregnancy failure[(3)]. The criteria used to diagnose early pregnancy failure vary. In the United Kingdom, guidelines state that the diagnosis of pregnancy failure may be established when the mean gestational sac diameter (GSD) exceeds 20 mm with no visible embryonic pole, or the embryonic crown-rump length (CRL) is greater than 6 mm with no detectable heart pulsation[(6,7)]. Others suggest that embryonic demise may be diagnosed when there is an empty gestational sac of 16 mm or a GSD greater than 16 mm[(8)]. Few studies are consistent with the presence of a yolk sac (YS) but no embryo when the GSD is greater than 25 mm and this can be considered a predictive factor of pregnancy failure[(9)]. In recent years, diagnostic advances of early pregnancy failure has determined the introduction of a new concept - Intrauterine pregnancy of uncertain viability (PUV), which is defined as the TVS visualization of a small intrauterine gestational sac without visible embryonic cardiac activity[(10)]. The anticipation of outcome in PUV is challenging[(6,8)], knowing the fact that gestational age cannot be confirmed with accuracy in the majority of cases[(11)].

Numerous studies have attempted to identify predictive factors of embryonic demise. Currently, ultrasound parameters are the most significant reported predictive factors.

Ultrasonographic prognostic factors

Gestational sac

The deciduo-placental interface and the exocelomic cavity are the first ultrasound evidences of a pregnancy that can be observed with TVS, starting from around 4.4-4.6 weeks of amenorrhea (32-34 days) when they reach together a size of 2-4 milimeters[(3)]. In a normal intrauterine pregnancy having 5-6 weeks of amenorrhea, the gestational sac grows at a rate of about 1-2 mm per day[(12,13)].

Gestational sac size is a good predictor of gestational age, and as the pregnancy progresses, normal

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development of the embryo and embryonic structures also occur until an embryo with cardiac activity is identified[14]. In normal pregnancies, embryonic heart pulsation can be usually detected once the sac measures at least 10 mm, and should always be seen above a critical discriminatory sac size. This discriminatory sac size has been proposed to be in the range of 20-30 mm using trans-abdominal scan, and in the range of 16-20 mm by means of transvaginal scans[15,16].

It was recognized that there is a wide range in GSD measurement in early intrauterine pregnancy. A hypotonic and smaller than expected gestational sac can predict a poor pregnancy outcome. However, another very important parameter like embryonic cardiac activity should be taken into consideration[17,18,19].

Crown-rump length

The main reference for the assessment of gestational age in early pregnancy is still a study published by Robinson and Fleming on CRL[20]. A smaller than expected CRL has been associated with subsequent miscarriage[21]. GSD:CRL ratios have also been used to predict pregnancy outcome with varying degrees of accuracy[22]. Although CRL growth is significantly different in viable and nonviable pregnancies, the interobserver variability in the measurements of CRL determines an operator to be cautious before assuming that a slow growing embryo will miscarry[23].

A study reporting inter and intra-observer variability of CRL measurements reveals a discriminative value of 6 mm for CRL for the first examination, translated to a range for a second examination from 5.4 mm to 6.7 mm, considering that the second evaluation is performed by another examiner . This study suggests that safe cut-off values to ascertain embryonic demise should be significantly wide to exclude any errors. Therefore, waiting 7-10 days in order to repeat a scan is proper in PUV and is highly unlikely to lead to physical harm. The anxiety associated with uncertainty regarding the status of pregnancy is extremely significant and should be counterbalanced by the possibility of pregnancy termination, which is definitely the most undesirable outcome for patients[24].

Yolk sac

The YS is the first structure that can be visualized inside the gestational sac, even before the embryo itself. This structure highlights since five weeks of amenorrhea or when the embryo reaches approximately 10 mm. The YS diameter increases slightly between 6 and 10 weeks of gestation and then decreases[25]. Following embryonic demise, the YS usually persist for several days. Ultrasonographic findings in PUV include a variety of aspects related to the YS, such as: nonexistent YS, quantitative alteration: small or hypoplastic YS, large or cystic YS, probably secondary to hydropic change and qualitative alterations: echogenic YS caused by necrosis, fibrosis or calcification. The YS is a structure of increasingly recognized importance in the initial mechanisms of pregnancy maintenance and the early growth and welfare of the embryo[26]. The variations in YS size and sonographic appearance in most abnormal pregnancies are probably the consequences of poor embryonic development or embryonic death rather than being the primary cause of early pregnancy failure[3].

Embryonic heart activity

Research has been published reporting the positive predictive value of ultrasonographic detection of embryonic heart activity in assessing pregnancy outcome. Studies can be broadly divided into those examining embryonic loss after confirmed embryonic cardiac activity, and those examining embryonic heart rate (EHR) in relation to outcome. EHR is the earliest proof of a viable pregnancy and there are findings that supports the idea that EHR decreases with increasing CRL[27].

Embryonic heart rate is known to rise from an average of 97.7 beats per minute at 36-38 days to 174.7 beats per minute at 60-62 days and EHR continues to raise about 4 beats per minute every day until 8 weeks of gestation. This suggests that EHR measurement by ultrasound may help in dating early first trimester pregnancy, and that first trimester bradycardia may be associated with a poor prognosis[28].

Identified characteristics in order to diagnose embryonic demise vary, but which ever cut-off values are used, the diagnosis of pregnancy loss is subsequently made if an embryonic heart beat is not visible on TVS after an interval of at least 7 days. This interval assessment aims to prevent the misdiagnosis of a potentially viable pregnancy as a miscarriage and thus minimizes the chance of inadvertent termination of pregnancy[9].

Ultrasonographic findings of early pregnancy

There is a lack of high-quality, prospective data on which to base guidelines for the accurate sonographic diagnosis of early pregnancy demise. The results are limited by the small number of studies and patients, the age of the studies and variable reference standards for diagnosis of early pregnancy demise[29]. However, the TVS technique has become an important tool in the evaluation of early pregnancy and contributed to new evidence regarding the evolution of pregnancy. The sonographic diagnosis of abnormal early pregnancy has been based on a variety of findings, which include the failure to depict a YS, a fetal pole and cardiac activity, or all of them at a designated gestational sac size[26]. Sonography can often confirm pregnancy failure after a single examination in pregnancies with amenorrhea longer than 7 weeks[30].

In early embryonic development, the embryo is detected immediately adjacent to the YS and the embryonic structure named yolk stalk has not yet developed[31,32,33]. If the embryo is separated from the YS, the separation is due to the development of the yolk stalk. As the yolk stalk length increases, the distance between embryo to the YS increases. For embryos with a CRL of 5 mm or less, there should be no separation of the embryo from the YS because the yolk stalk is yet nonexistent. In some pregnancies with small embryos, there is an

unexpected separation of the embryo from the yolk sac[4]. When the embryo reaches 5 mm in CRL there is an observable separation between the embryo and YS caused by stalk development. Thus, when a separation is observed, one should invariably detect a heartbeat, whereas the absence of a heartbeat should confirm pregnancy failure[34].

The depiction of separation of an embryo with a CRL of 5 mm or less from the YS indicates development of a yolk stalk and thus a more advanced stage of gestation can be deduced from the CRL alone. The yolk stalk sign is valuable in predicting early pregnancy failure whether used independently or in combination with other abnormal features[35].

Hormones levels in early pregnancy failure - a predictive factor?

Ultrasonographic technique is dependent upon the skill of the operator and thus the results are not always consistently reproducible. In addition to this technique, another sensitive and specific biomarker is required to determine the pregnancy viability for early pregnancy termination[36].

Progesterone is a 21 carbon steroid hormone secreted by corpus luteum of the ovary. This hormone is an important promoting factor for endometrial decidualization, preparing the uterus for implantation of the blastocyst and to maintain the pregnancy. The physiological functions of progesterone include inhibition of smooth muscle contractility and inhibition of immune responses like those involved in graft rejection[37]. Obviously, it is essential to study women after natural conceptions without exogenous progesterone support, while evaluating the relation between serum progesterone and viability of the first trimester pregnancy[38,39]. Recent studies suggest that serum progesterone measured in early pregnancy is the most powerful single predictor of pregnancy outcome in natural conceptions[1,40].

Beta-huma chorionic gonadotropin (β-hCG) is also a major embryonic "signal" that plays a critical role in the initiation and maintenance of pregnancy[4]. β-hCG acts on the intrauterine environment via the luteinizing hormone/hCG receptor. At the time of implantation, βhCG has been shown to be involved in a wide spectrum of cell targets and biological actions. Synthesized early by the trophoblast, hCG appeares to influence endometrial receptivity and implantation, to promote decidualization of human endometrial stromal cells[41] and to possess both direct and indirect angiogenic properties[42,43,44].

There are studies that concluded that serum progesterone level combined with β-hCG measurements, with a highly accuracy, had the best prognostic reliability for predicting the outcome of embryonic demise compared to serum progesterone alone or β-hCG alone[45]. Others studies founded that the mean serum progesterone was significantly high for viable pregnancies (22.1 ng/ml) as compared to non-viable pregnancies (10.1 ng/ml) and they concluded that a serum progesterone assay alone is predictive of pregnancy outcome especially during the first 8 weeks of gestation[46]. There are also other studies that reinforces the idea of serum progesterone alone being a reliable marker for prediction of early pregnancy failure[39].

Conclusions

The YS sign is valuable in predicting early pregnancy failure whether used independently or in combination with other abnormal ultrasonographical features. It is necessary an evaluation of the positive predictive value of TVS relating the yolk stalk for predicting early pregnancy failure for an embryo with a CRL of 5 mm and no detectable heartbeat.

Biomarkers, such as progesterone or β-hCG can be predictive factors for early pregnancy failure, requiring further studies to sustain the idea that they could be of greater value separately or together. ■

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