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human reproduction **OPINION**

Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group

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ABSTRACT: Pregnancy loss prior to viability is common and research in the field is extensive. Unfortunately, terminology in the literature is inconsistent. The lack of consensus regarding nomenclature and classification of pregnancy loss prior to viability makes it difficult to compare study results from different centres. In our opinion, terminology and definitions should be based on clinical findings, and when possible, transvaginal ultrasound. With this Early Pregnancy Consensus Statement, it is our goal to provide clear and consistent terminology for pregnancy loss prior to viability.

Key words: pregnancy loss / non-visualized pregnancy loss / ectopic pregnancy / miscarriage / recurrent pregnancy loss

Introduction

The lack of a consistent and generally accepted terminology, and strict definitions of adverse pregnancy outcomes, makes it difficult to compare scientific results from different research groups in early pregnancy. In this Consensus Statement from the ESHRE Special Interest Group, Early Pregnancy, we present our recommendations for pregnancy terminology and definitions for adverse pregnancy outcome before viability. We aimed to provide a clear, consistent and widely applicable terminology for early pregnancy research. Table I summarizes our recommendations for a standardized terminology.

What is a pregnancy loss?

Under normal, non-neoplastic conditions, human chorionic gonadotrophin (hCG) is exclusively produced by the syncytiotrophoblast. It follows logically that a *pregnancy loss* is the spontaneous demise of a pregnancy, which has been confirmed by at least two positive β-hCGs in the serum or urine.

Embryology and ultrasound

The general availability of high-resolution transvaginal ultrasound in developed countries, combined with sensitive urine and serum β-hCG measurements, has revolutionized the diagnosis of pregnancy in very early gestation. Estimates of gestational age should be based on transvaginal ultrasound, whenever possible.

Non-visualized pregnancy loss

Any pregnancy loss, which has not been confirmed ultrasonically or histologically, should be classified as a *non-visualized pregnancy loss*, irrespective of the time passed since the last menstrual period or clinical presentation.

If the pregnancy has been diagnosed only by either serum or urine β-hCG, and the serial results decrease to negative, the pregnancy loss should be termed a *biochemical pregnancy loss*. We recommend against the use of the term 'chemical pregnancy loss' since it is a biological process.

When transvaginal ultrasound evaluation fails to determine the localization of a pregnancy, it is initially classified as a *pregnancy of unknown*

Table I Terminology for classifying pregnancy failure prior to viability for research purposes.

Term	Description of pregnancy loss and clinical or ultrasound findings	References
Pregnancy loss	Spontaneous pregnancy demise	
Early pregnancy loss	Spontaneous pregnancy demise before 10 weeks of gestational age (before 8th developmental week)	
Non-visualized pregnancy loss	Spontaneous pregnancy demise based on decreasing serum or urinary β-hCG levels and non-localization on ultrasound, if performed	Kolte *et al.* (2014)
Biochemical pregnancy loss	Spontaneous pregnancy demise based on decreasing serum or urinary β-hCG levels, without an ultrasound evaluation	Farquharson and Stephenson (2010)
Resolved pregnancy loss of unknown location (resolved PUL)	Pregnancy demise not visualized on transvaginal ultrasound with resolution of serum β-hCG after expectant management or after uterine evacuation without chorionic villi on histology	Barnhart *et al.* (2011)
Treated pregnancy loss of unknown location (treated PUL)	Pregnancy demise not visualized on transvaginal ultrasound with resolution of serum β-hCG after medical management	Barnhart *et al.* (2011)
Miscarriage	Intrauterine pregnancy demise confirmed by ultrasound or histology	ASRM Practice Committee (2013) and Stephenson and Kutteh (2007)
Early miscarriage	Intrauterine pregnancy loss $<$10 weeks' size on ultrasound	
Anembryonic (empty sac) miscarriage	Intrauterine pregnancy loss with a gestational sac but without a yolk sac or an embryo on ultrasound	
Yolk sac miscarriage	Intrauterine pregnancy loss with a gestational sac and yolk sac, without an embryo on ultrasound	
Embryonic miscarriage	Intrauterine pregnancy loss with an embryo without cardiac activity on ultrasound	
Fetal miscarriage	Pregnancy loss $\geq$10 weeks' size with a fetus ($\geq$33 mm) on ultrasound	Stephenson and Kutteh (2007)
Ectopic pregnancy	Ultrasonic or surgical visualization of a pregnancy outside of the endometrial cavity	Barnhart *et al.* (2011) and Barnhart (2009)

location (PUL). With further evaluation, final outcomes of PULs can be categorized into ectopic pregnancy, intrauterine pregnancy, resolved PUL or treated PUL. *Resolved PUL* is defined as decreasing β-hCG to negative, either spontaneously or after uterine evacuation without chorionic villi on pathology. *Treated PUL* is defined as a PUL treated medically (usually with methotrexate). Major efforts have gone into the classification of PULs and their final diagnoses, the scope of which is beyond this paper (Barnhart *et al.*, 2011).

We discourage the use of terms like 'preclinical miscarriage' (Macklon *et al.*, 2002) as it is ambiguous and assumes the pregnancy is within the uterine cavity. If a woman does not seek medical assistance in the course of a pregnancy loss, except for confirmation of pregnancy with a urine or serum β-hCG, biochemical pregnancy loss is the most appropriate term, unless tissue is passed and confirmed histologically.

Ectopic pregnancy

If the pregnancy is visualised outside the uterine cavity, either by ultrasound or histologically after surgery, the pregnancy is an *ectopic pregnancy*. Ectopic pregnancies can be further divided into subgroups based on ultrasonic findings. These are beyond the scope of this paper, but have been reviewed by Barnhart (Barnhart, 2009).

Intrauterine pregnancy loss

Though fetal growth rates may vary according to various maternal characteristics (van Uitert *et al.*, 2013), in normal pregnancies, early embryonic development is relatively uniform and, therefore, we can use developmental milestones identified on transvaginal ultrasound (Doubilet *et al.*, 2013). Failure to meet these milestones can be useful in determining gestational age at the time of miscarriage, making ultrasound findings an important component of early pregnancy evaluation (Farquharson and Stephenson, 2010).

For intrauterine pregnancy demise before 10 weeks of gestation, we recommend the term *early miscarriage* comprising *anembryonic* (*empty sac*), *yolk sac* and *embryonic miscarriages* (Table I).

The term *early miscarriage* covers all three types of intrauterine pregnancy losses, as described above. Clinically, patients may benefit emotionally from knowing when the pregnancy demise occurred, based on ultrasound findings (Nikcević *et al.*, 2007). For research purposes, these more detailed descriptions of intrauterine pregnancy losses may lead to a better understanding of the pathophysiology, and developmental-age specific causation.

We recommend the abandonment of the old fashioned term, *blighted ovum*, as it is poorly defined in the literature (Goldstein, 1990). Patients prefer the word 'miscarriage' rather than '(spontaneous) abortion' because of its lay person's connotation (Silver *et al.*, 2011). Physicians as well as patient organizations have advocated this change for decades (Gardner, 1972; Beard *et al.*, 1985; Harison, 1986; Pridjian and Moawad, 1989; Chalmers, 1992; Hutchon and Cooper, 1998; Cameron and Penney, 2005; Farquharson *et al.*, 2005; Jutel, 2006; Silver *et al.*, 2011; Moscrop, 2013), but 'spontaneous abortion' is still used in scientific literature. In the journal *Human Reproduction*, at least

11 papers using the term 'spontaneous abortion' have been published between 1 January 2013 and June 2014, despite the preference of the journal to use the term 'miscarriage'.

At the end of the seventh developmental week, which equates to the end of the ninth gestational week, organogenesis is complete; this heralds the end of the embryonic period and the beginning of the fetal period. We recommend that a fetal demise of at least 10 weeks of gestation, and before the fetus could survive ex utero, is termed a *fetal miscarriage*. Since factors associated with early miscarriage and fetal miscarriage may differ, a clear distinction between these types of miscarriages should be made. Traditionally, the distinction between 'early' (first trimester) and 'late' (second trimester) miscarriage has been at 12 weeks of gestation; to our knowledge this has been based on neither ultrasound findings nor biological processes.

Therefore, striving to base terminology and definitions on human development, we recommend the use of 'early' and 'fetal' miscarriage, based on ultrasound findings, as described above. This will move research forward, leading to an understanding of why pregnancy loss occurs at specific developmental milestones.

Recurrent pregnancy loss

Recurrent pregnancy loss is a heterogeneous reproductive problem, with multiple aetiologies and contributing factors. As such, evaluating and treating women with this condition is a complex task, and research in the field is no less daunting. The definition of recurrent pregnancy loss is debated, ranging from two clinical miscarriages, not necessarily consecutive, according to the American Society for Reproductive Medicine (ASRM) (ASRM Practice Committee, 2013) and a joint International Committee for Monitoring Assisted Reproductive Technology and World Health Organization glossary (Zegers-Hochschild *et al.*, 2009), to three consecutive pregnancy losses (not necessarily intrauterine) as defined by both the European Society for Human Reproduction and Embryology (Jauniaux *et al.*, 2006) and the Royal College of Obstetricians and Gynaecologists (RCOG Green Top Guideline, 2011).

In the latest ASRM Practice Committee Opinion on the definition of recurrent pregnancy loss, a pregnancy is defined 'as a clinical pregnancy documented by ultrasonography or histopathologic examination' (ASRM Practice Committee, 2013). However, we recently showed that for women with idiopathic RPL, defined as three or more consecutive pregnancy losses before 12 weeks' gestation, non-visualized pregnancy losses (biochemical pregnancy losses and/or resolved and treated pregnancies of unknown location) had the same prognostic impact for future live birth as a clinical miscarriage (Kolte *et al.*, 2014). Therefore, non-visualized pregnancy losses should be included in the definition of *recurrent pregnancy loss*.

Recurrent pregnancy loss or recurrent miscarriage?

With the above-mentioned terminology in mind, we recommend the term *recurrent pregnancy loss* be used to describe repeated pregnancy demise, and the term *recurrent miscarriage* be used when all pregnancy losses have been confirmed as intrauterine miscarriages, by ultrasound or histology. In research literature, the (mean or median) number of pregnancy losses and/or miscarriages should always be mentioned. As mentioned, the definition of recurrent pregnancy loss and recurrent miscarriage is controversial, but it is our opinion that the accurate reporting of clinical data is the first step towards an evidence-based definition of recurrent pregnancy loss.

Conclusions

In order to make meaningful comparisons between scientific studies, it is paramount that definitions are adequately described and adhered to. Whenever possible, pregnancy losses should be classified into at least groups of non-visualized pregnancy losses, early miscarriage, fetal miscarriage, ectopic pregnancy, stillbirth or neonatal death. Furthermore, we strongly advise researchers and clinicians to clearly describe the type of pregnancy loss, and additionally, gestational age, number of pregnancy losses, and relevant details of ultrasound measurements.

This Consensus Statement should bring us closer to using clear, consistent and widely applicable terminology for early pregnancy research.

Authors' roles

A.M.K. co-initiated the project, participated in discussions of content at meetings in Brussels, November 2013 and Munich, July 2014 and wrote the manuscript; L.A.B. co-initiated the project and critically revised the manuscript; O.B.C., R.G.F., S.Q. and M.G. participated in discussions of content and critically revised the paper; M.D.S. initiated the project, participated in discussions of content and critically revised the manuscript.

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Conflict of interest

None declared.

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