

Macroscopic and microscopic morphology of first trimester miscarriage and subsequent pregnancy outcome - An exploratory study



Isabelle M.A. van Gruting, MD ^a, Moira A. Müller, MD PhD ^a, Krijn van Groningen, MD ^b, Niek Exalto, MD PhD ^{c,*}

^a Department of Obstetrics and Gynaecology, Spaarne Gasthuis, Spaarnepoort 1, 2134 TM, Hoofddorp, The Netherlands

^b Department of Clinical Pathology, Spaarne Gasthuis, Spaarnepoort 1, 2134 TM, Hoofddorp, The Netherlands

^c Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine, Erasmus MC: University Medical Centre Rotterdam, 's-Gravendijkwal 230, 3015 CE, The Netherlands

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ABSTRACT

Introduction: Reduced chorionic villous vascularization is associated with first trimester miscarriage and second trimester fetal loss. Differences in villous vascularization have been observed in combination with complications in the third trimester of pregnancy. The aim of this study was to investigate whether abnormal morphology and reduced chorionic villous vascularization in first trimester miscarriages are associated with an increased risk on adverse outcome and/or pregnancy complications in subsequent pregnancy. Secondly, to assess the influence of these parameters on the length of the interpregnancy interval and infertility.

Methods: In a retrospective cohort study 134 consecutive women who underwent dilatation and curettage for a miscarriage were included. The degree of chorionic villous vascularization in miscarriage tissue was determined by a pathologist. Ultrasound details of these miscarriages and clinical data on the subsequent pregnancy of these women were obtained.

Results: Neither reduced vascularization nor early embryonic arrest in first trimester miscarriages are associated with an increased risk of a subsequent miscarriage or adverse obstetric and perinatal outcome of subsequent pregnancy. Abnormal morphology of the first trimester miscarriage did not influence the time to subsequent pregnancy. A shorter mean interpregnancy interval between miscarriages was observed after miscarriages with reduced chorionic villous vascularization (5.5 vs. 10.7 months; $p = 0.051$), showing a trend towards an association.

Discussion: Chorionic villous vascularization and morphology have no influence on subsequent pregnancy outcome. Therefore it remains unknown what aspects of miscarriage are causing the increased risk on subsequent miscarriage and complications in the third trimester of the subsequent pregnancy.

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1. Introduction

First trimester miscarriages are classified as empty sac miscarriages, yolk sac miscarriages or embryonic miscarriages and are more often due to abnormal embryonic development with or without chromosomal abnormalities, rather than to a maternal

inability to maintain a normal pregnancy. Abnormal embryonic development, resulting in an early embryonic arrest, is often associated with reduced chorionic villous vascularization, being more pronounced in empty sac miscarriages than in embryonic miscarriages [1–4].

Furthermore, second trimester fetal loss is associated with a reduced peripheral chorionic villous vascularization [5]. The demonstrated reduction of placental vascularization and placental weight in these pregnancies implies that the process of vasculogenesis and angiogenesis is already disturbed early in pregnancy. Intrauterine growth restriction (IUGR), hypertensive disorders and

* Corresponding author. Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine, Erasmus MC: University Medical Centre Rotterdam, PO box 2040, Room Na-1517, 3000 CA Rotterdam, The Netherlands.

E-mail address: n.exalto@erasmusmc.nl (N. Exalto).

absent or reversed end-diastolic blood flow (ARED) in the umbilical artery in the second and third trimester of pregnancy are associated with different vascularization patterns in the placenta, already existing in the first trimester [6,7].

It is known that the frequency of normal embryonic karyotypes significantly increases with the number of previous miscarriages and a normal karyotype in a previous miscarriage is a predictor for a subsequent miscarriage [8]. The cumulative live birth rate after recurrent miscarriage caused by abnormal karyotype was significantly higher (71.9% vs. 44.7%) in comparison to euploid miscarriages [9]. We therefore hypothesised about a possible predictive value of other miscarriage characteristics regarding the outcome of subsequent pregnancy. It has also been suggested that recurrent miscarriage, often characterized by a short interpregnancy interval, may be caused by an insufficient selection during implantation, allowing abnormal pregnancies to continue [10].

The aim of this exploratory study was to investigate the influence of abnormal morphology and reduced chorionic villous vascularization in first trimester miscarriages on adverse outcome and/or pregnancy complications in subsequent pregnancy. The secondary aim was to investigate the influence of these parameters on the length of the interpregnancy interval and infertility.

2. Material and methods

2.1. Patient selection

In this study 144 women were included who underwent a dilatation and curettage (D&C) between January 2008 and December 2010 and in whom the degree of chorionic villous vascularization was determined. All records of these women were retrospectively retrieved and demographic data were obtained. The study population consisted of miscarriages ($n = 134$) and terminations of pregnancy ($n = 10$).

2.2. Histology

The degree of vascularization was determined using a scoring system, which has previously been validated by establishing agreement between four observers with varying experience. This scoring system has shown to have a good to excellent interobserver agreement in histological scoring (kappa 0.64–0.86) [3]. The specimens were examined routinely by an experienced pathologist and chorionic villous vascularization was scored as follows (Fig. 1):

- Grade 0 unknown, there are an insufficient number of villi available for evaluation;
- Grade I normal, vessels with nucleated blood cells are present in almost every (at least 9 out of 10) villous, have a very clear appearance and are located centrally as well as peripherally (in contact with the trophoblastic layer), in some villi the number of vessels is even numerous (>5);
- Grade IIA mild hypoplasia, vessels with nucleated blood cells are not present in all villi, less numerous and predominantly located centrally;
- Grade IIB severe hypoplasia, villi are predominantly avascular, however, in a single villous, a vessel is present with one or more nucleated blood cells;
- Grade III avascular, all villi are avascular, although sporadically a very small vessel, with or without a nucleated blood cell may be present.

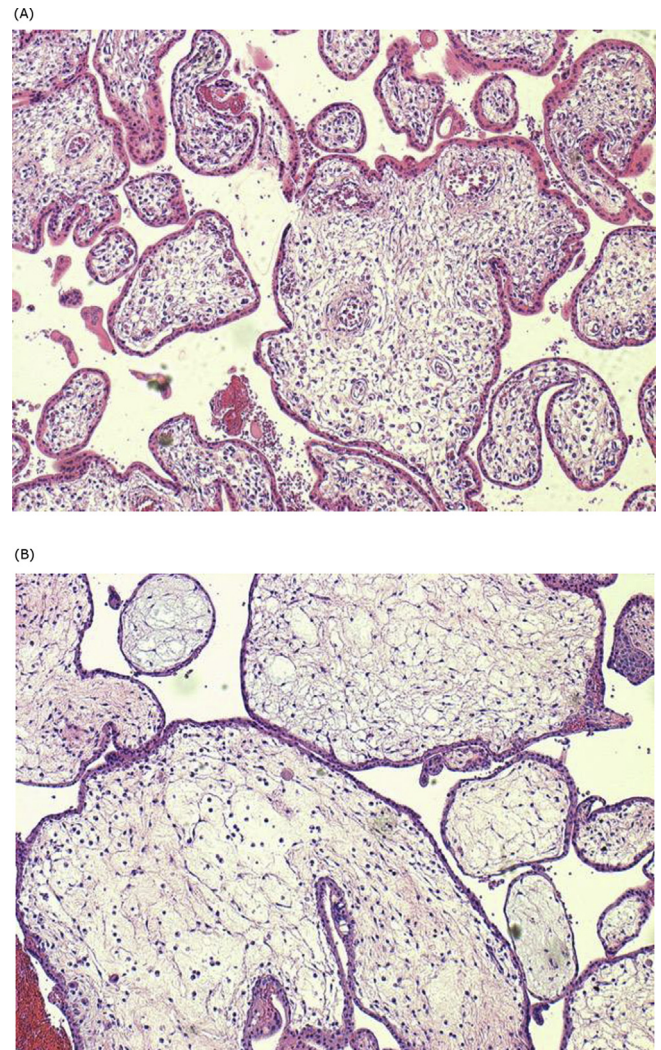


Fig. 1. First trimester chorionic villi with (A) Grade I normal vascularization and (B) Grade III avascular villi.

2.3. Ultrasound criteria

Information on the ultrasound assessment prior to the D&C was obtained. Data on the presence or absence of the gestational sac, yolk sac, embryo, cardiac activity, the gestational diameter of the sac (GDS) and the crown-rump-length (CRL) were collected if available. An *empty sac miscarriage* is defined as an intrauterine pregnancy loss with a gestational sac but without a yolk sac or an embryo on ultrasound (GDS >8 mm, embryonic arrest ± 28 days gestational age (GA)). A *yolk sac miscarriage* is defined as an intrauterine pregnancy loss with a gestational sac and yolk sac, without an embryo on ultrasound (GDS >16 mm, embryonic arrest ± 35 days GA). An *embryonic miscarriage* is defined as an intrauterine pregnancy loss with an embryo without cardiac activity on ultrasound (CRL ≥ 5 mm, embryonic arrest after ± 42 days GA) [11]. A *viable pregnancy* is defined as an embryo of at least 5 mm with cardiac activity.

2.4. Data collection of subsequent pregnancy

The ten women with a viable pregnancy, who chose to have the pregnancy terminated, were excluded from further analysis leaving a miscarriage group of 134 cases. Demographic data and data

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