

Article Type: Mini-commentary

Mini-commentary on 2017-OG-20389R1: Extra-villous trophoblast invasion in placenta accreta is associated with differential local expression of angiogenic and growth factors: a cross sectional study

### **Placenta accreta spectrum: A need for more research on its etiopathogenesis**

Eric Jauniaux<sup>1</sup>, Graham J Burton<sup>2</sup>

1. EGA Institute for Women's Health, University College London Faculty of Population Health Sciences, University College London, UK. e.jauniaux@ucl.ac.uk
2. The Centre for Trophoblast Research, Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, United Kingdom.

Placenta accreta is a pathologic condition of early placentation that has been studied by clinicians and pathologists for nearly 100 years. The main effect is a loss of the normal plane of cleavage from the uterine wall, resulting in massive haemorrhage when attempts are made at removing the placenta manually at delivery. Excessive remodelling of the radial and arcuate arteries in the invasive forms of placenta accreta spectrum increases the risk of complications (Jauniaux et al., *AJOG*, 2018;218:75-87).

The oldest hypothesis for the development of placenta accreta was based on a theoretical primary defect of the trophoblast leading to excessive villous invasion of the myometrium. Recent histopathologic studies have found that in placenta accreta spectrum

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.15194

This article is protected by copyright. All rights reserved.

Accepted Article

the villous tissue, and in particular its trophoblast, shows no morphological changes compared to non-accreta placentas, even in the invasive areas. The morphological changes observed in the extravillous trophoblast are probably environmental, and the consequence of an unusual and prolonged interaction with the highly vascularised deep myometrium which these cells would not normally reach (Jauniaux and Jurkovic, *Placenta* 2012;33:244–51).

Overall, compared to other placental-related disorders of pregnancy, such as pre-eclampsia or fetal growth restriction, there have been few studies of the etiopathogenesis of this complex disorder of placentation. One of the reasons why there are limited data is that until the major rise in caesarean rates in the last two decades the prevalence of placenta accreta spectrum, and in particular of its invasive forms, was low. The limited use by most authors of cohort studies on prenatal diagnosis, management and outcome of standardised clinical and imaging diagnostic criteria and terminology have led to conflicting results. Furthermore, although in >90% of cases diagnosed prenatally or at birth the management has been a caesarean hysterectomy, most cohort studies did not include detailed data on histopathology. In particular, there is a lack of data on the depth of invasion of the accreta villous tissue (Jauniaux et al., *AJOG* 2016;215:712-21) which is essential for the differential diagnosis between simply adherent and invasive cases, and thus for the interpretation of clinical and histopathologic data.

Immunohistochemical data have indicated that abnormal villous adherence develops as a result of abnormal expression of growth-, angiogenesis- and invasion-related factors in the different trophoblast sub-populations (Jauniaux and Burton, *Clin Obstet Gynecol* 2018;61:in press). The findings of Duzyi et al (*BJOG* 2018; in press) add to these findings. Although some are hard to interpret, for example, the immunostaining for HIF1 $\alpha$  is cytoplasmic rather than nuclear suggesting it may not be signalling, they support the modern hypothesis that accreta placentation results from a post-surgical defect of the endometrial-myometrial interface leading to a failure of decidualisation in the area of the uterine scar, allowing for abnormally deep placentation. Placenta increta and percreta are not due to

further invasion of trophoblastic cells into the uterine wall. They likely arise secondary to the dehiscence of a scar, leading to the presence of anchoring villi deep within the uterine wall (Figure 1), giving them greater access to the deep uterine vasculature.

**Disclosure of interests**

The authors declare no conflicts of interest. Completed ICMJE disclosure forms are available to view online as supporting information.

**Figure.** Microscopic view of the placental bed from a hysterectomy specimen at 32 weeks in a pregnancy complicated by placenta previa increta (H&E x 10) showing the disruption of the decidua by placental villi (arrow) invading the deep myometrium (M).

