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Placenta Accreta: A Review of Current Advances in Prenatal Diagnosis

C. Mazouni [a,*], G. Gorincour [b], V. Juhan [b], F. Bretelle [a]

[a] Department of Obstetrics and Gynecology, Conception Hospital, Marseille Public Hospital System, 147 boulevard Baille, 13385 Marseille, France
[b] Department of Radiology, Timone Hospital, Marseille Public Hospital System, 147 boulevard Baille, 13385 Marseille, France

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Abstract

Placenta accreta is a life-threatening obstetrical condition requiring a multidisciplinary approach. Despite identified obstetrical risk factors, the diagnosis is often made at the time of delivery. Recent advances in biology could allow a prenatal screening of placenta accreta with the identification of biological markers in maternal blood including cell-free fetal DNA, placental mRNA, and DNA microarray. These promising technologies can detect the presence of anomalies and should play a future role in developing a better understanding of placental invasion.

Ultrasound imaging is popular due to its low cost and accessibility and widely used for the screening of placenta location and potential abnormal development. This exam is associated with high sensitivity and specificity for diagnosis of placenta accreta when specific defined criteria are used for the diagnosis. A placental MRI provides a morphological description, as well as recently demonstrated topographical information that optimizes diagnosis and surgical management.

The screening of placenta accreta should be improved with the use of a combination of these diagnostic techniques and benefit high-risk populations with a reduction in morbidity.

Keywords: Accreta; Fetal DNA; Placental mRNA; Placenta; MRI; Ultrasound

1. Introduction

Placenta accreta is defined as an abnormal adherence of a part of the placenta, or the entire placenta, to the uterine wall with a partial or complete absence of the decidua basalis. The placenta may not only be abnormally adherent to the uterine wall (myometrium), but it can also invade other tissues (i.e., uterine serosa or bladder) and becomes impossible to separate out. Despite promising results with a conservative approach that leaves the placenta in the uterus [1], the standard treatment is hysterectomy with hypogastric artery ligation or embolization.

The reported incidence of placenta accreta is 1 per 2500 deliveries [2]. Identified risk factors include maternal demographic factors such as grand multiparity and age; as well as, obstetrical factors such as history of uterine surgery, placenta praevia, and previous cesarean sections [2,3]. The growing trend in cesarean sections [4] correlates with an increase in the incidence of placenta accreta of up to 5% in women who have had a previous cesarean section [5] and up to 67% with the association of placenta praevia and cesarean section [6]. Unfortunately, this life threatening obstetrical condition is generally diagnosed at the time of delivery, often resulting in emergency treatment with a greater risk of morbidity. In contrast, a prenatal diagnosis would allow for a planned approach with the possibility of treatment under more controlled conditions, and could also reduce the blood loss associated with placenta accreta during delivery [7,8]. Therefore, optimal management must involve a multidisciplinary approach that includes obstetricians, radiologists, and anesthetists.

* Corresponding author. Tel.: +33 4 9138 3775; fax: +33 4 9138 3030.
E-mail address: chafikamazouni@yahoo.fr (C. Mazouni).

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The development and advances of imaging and biological techniques can lead to reduce related morbidity and optimize the management of invasive placenta. This review discusses some of the recent advances in biology and radiology for the prenatal diagnosis of placenta accreta.

2. Biological markers of placenta accreta

It is intuitively appealing to hypothesize that maternal blood analysis might yield information on abnormal placenta development. Several biological factors like creatine kinase levels [9] or elevated levels of alphafetoprotein [10,11] have been described in the past to reflect placental dysfunction, but these hypotheses have not been confirmed. Three biological markers or techniques have recently been described as potential tools for the diagnosis of placental abnormalities: cell-free fetal DNA, placental mRNA, and DNA microarray.

2.1. Cell-free fetal DNA

Advances in molecular biology have furthered the exploration of placental function with the detection of cell-free fetal DNA in maternal blood. Since the report of Lo et al. [12], who first described the presence of fetal DNA in maternal plasma and serum, the potential application of this discovery has been explored in various obstetrical diseases including pre-eclampsia [13] and chromosomal anomalies [14]. The screening test is based on DNA extraction and real-time polymerase chain reaction (PCR) amplification to detect fetal DNA in maternal blood.

Various hypotheses have been suggested to explain the presence and origin of fetal DNA in maternal blood. From the various potential tissues sources explored: fetal haematopoietic cells [12,15], the placenta [16,17], and direct feto-maternal transfer of DNA molecules [18], the cell-free fetal DNA was demonstrated to originate from apoptotic villous trophoblasts [19]. The increase in cell-free fetal DNA in maternal blood occurs consecutively with the invasion of trophoblasts into the uterine muscle. This phenomenon is attributable to the maternal immune response to the uterine muscle invasion that leads to trophoblast destruction [20]. Sekizawa et al. [20] suggested that dysfunctional and thin deciduas may explain the increase in placenta praevia cases. In their study, a higher concentration of fetal DNA (DYS14) was observed in the placenta praevia group than in the control group (294.3 genome-equivalents/mL *vs*. 184.2 genome-equivalents/mL, $p = 0.015$) [20]. Moreover, the two patients diagnosed with invasive placenta had respective concentrations of 609.6 and 582.0 genome-equivalents/mL. Thus, despite the limitation of the study due to a small population size, fetal DNA appeared to be a promising marker of abnormal placenta implantation.

Fetal DNA concentration in maternal blood has also been used to monitor post delivery levels in the event of a retained placenta [21]. Apart from Invernizzi et al.'s study [22], who reported persistence of fetal DNA several years after delivery, most publications documented a rapid disappearance of fetal DNA from blood after uncomplicated deliveries [23–27]. For example, Rijnders et al. did not observe the presence of cell-free fetal DNA in the blood from 120 non-pregnant women, 82 of whom had experienced previous pregnancy [24]. Benachi et al. confirmed these data, as the SRY gene was not observed in sera from non-pregnant women, or women carrying a female fetus who had a history of a previous male infant [25]. Similar data were reported by Smid et al. who did not detect fetal DNA in plasma from non-pregnant women or female-bearing pregnant women [26]. The authors did observe a subgroup of 13 patients who were initially positive for SRY, however a rapid decrease of SRY amplification level was observed 1–5 days after delivery. A postpartum analysis of blood from 17 women with high levels of male fetal cells, confirmed the rapid clearance of cell-free DNA after delivery [27]. The main hypothesis to explain the discordant results of Inverzzini et al. is that there may have been a potential contaminant or error in the preparation of samples and measurement, as well as the use of improper statistical analyses [27].

2.2. Placental mRNA

The recent discovery of mRNA of placental origin in maternal plasma serum provides new possibilities in exploring placental dysfunction. Using real-time quantitative PCR, Ng et al. [28] reported respective increasing and decreasing detection rates of hPL mRNA and βhCG mRNA with gestational age. The level of detection of mRNA is higher in early pregnancy with a rate of 100% compared to the 7.7% in late pregnancy.

Ng's study of mRNA clearance showed undetectable levels in the immediate post delivery period involving uncomplicated pregnancies [28]. Masuzaki et al. [29] proposed to use placental mRNA to monitor placental status after methotrexate use in placenta accreta. In their study, Masuzaki et al. [29] reported the case of a woman diagnosed with placenta percreta with a residual placental mass in the internal OS and treated with methotrexate. The βhCG mRNA and hPL mRNA levels measured after methotrexate treatment corresponded with the decreasing hCG protein concentration. In addition, the expression patterns of βhCG mRNA and hPL mRNA were reflective of their respective tissue origin, i.e., proliferating cytotrophoblasts and mature syncitiotrophoblats.

2.3. DNA microarray

The principle of DNA microarray technology is based on high-throughput analysis of gene function. DNA microarray is a remarkable tool used to quantify thousands of mRNA species in a small tissue sample in a single experiment. RNA is extracted from tissues samples, amplified and reverse transcribed. Microarray experiments require between 10 and 40 μg of high-quality RNA. This RNA is hybridized to known DNA fragments in the microarray to identify expressed genes. DNA microarray permits gene structure identification and expression level determination in a specific disease condition, for instance in the growth restricted fetuses [30]. This technique provides a new approach to placental status assessment