Time to reconsider elective Cesarean birth

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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: 10.1002/uog.22158

Abnormally invasive placentation (AIP) is a recognized leading cause of peripartum hemorrhage, operative intervention and related maternal morbidity and mortality. This is particularly the case in low-resource medical settings, where AIP is also associated with increased perinatal morbidity and mortality secondary to increased prevalence of preterm birth and small for gestational age fetuses[1]. Although all-cause maternal mortality worldwide has declined in the last two decades, the incidence of AIP has increased 10-fold over the last five decades such that it is now estimated that 1/500 to 1/2500 deliveries are complicated by morbid placental adherence. The increase in incidence of AIP has been attributed to the increasing Cesarean section rate, which is directly linked to AIP's transition from what was once rare, to an increasingly common complication of pregnancy[2,3].

Adverse outcome of AIP is critically dependent on whether it is diagnosed antenatally, as the maternal morbidity and mortality of AIP, which is diagnosed at birth, is significantly higher. Therefore, the key to good management of AIP is screening of high-risk groups and diagnosis of AIP prior to the onset of labor so as to enable scheduled birth under optimal conditions. An antenatal screening program for AIP should involve identifying women at risk of AIP according to features in their medical history or findings in the current pregnancy, followed by ultrasound assessment to confirm or refute the diagnosis of AIP – with or without complimentary MRI to ascertain degree of extrauterine involvement. Despite significant research contributions and recent clinical advances in the use of imaging to diagnose AIP, a large proportion of AIPs often remain unidentified antenatally – presumably because effective screening strategies are lacking. We contest that a poor understanding of the pathophysiology of AIP underlies the absence of effective prevention or

screening for AIP. In this opinion piece, we discuss an important contributor to the rising incidence of AIP and potential solutions to manage this problem.

Cesarean birth and development of AIP

The original hypothesis suggested that AIP develops secondary to over-aggressive trophoblastic invasion or defective decidual function. It is now increasingly believed that AIPs form as a consequence of scar implantation - a result of placental implantation into an iatrogenically defective decidua. Decidual defects typically occur secondary to endometrial trauma following Cesarean section, other uterine surgical procedures or intrauterine infection[4–6].

Several pre-pregnancy risk factors have been associated with AIP, such as advanced maternal age, parity, short inter-pregnancy interval, obesity, smoking, in-vitro fertilization and previous uterine surgery. Placenta previa is the main risk factor in the current pregnancy to significantly increase the risk of AIP. At first glance, it is difficult to rationalize the mechanism for how this myriad of risk factors predispose to AIP. Evidence from large epidemiological studies have demonstrated that the majority of the risk factors are confounders by virtue of being proxy markers for either previous Cesarean birth or placenta previa. The combination of a low-lying placenta and previous Cesarean section has been found to be the strongest risk factors for AIP (Table 1)[7–12]. It is likely that maternal age, obesity and parity are proxies for increased risk of Cesarean birth, whilst embryo replacement in IVF predisposes to low uterine implantation and subsequent placenta previa[13,14].

Number and timing of Cesarean birth

Original studies suggested that the risk of AIP increases with the number of Cesarean births[2,10,15]. The presumed causation was linked to the number of post-

Cesarean decidual scars in the uterus increasing the likelihood of a scar pregnancy. Subsequent systematic reviews demonstrated that the increase in risk for AIP plateaus after the second Cesarean birth, calling into question the hypothesis for AIP pathophysiology based purely on the number of decidual defects[12]. More recent epidemiolocal data has suggested that AIP is most strongly associated with elective Caesarean birth, rather than the emergency Caesarean birth or number of Caesareans section[16,17]. Compared to emergency Cesarean birth, pre-labor elective Cesarean section significantly increased the risk of AIP in a subsequent pregnancy with placenta previa by three-fold[16] (Table 1). Typically, the second or third Cesarean sections are scheduled and conducted pre-labor, explaining the plateau after the second Cesarean birth and making number of Cesarean births a confounder[12].

To date, the predisposition to AIP after elective (pre-labor) Caesarean birth has not had a rational biological explanation. We hypothesized that this clinical observation could be explained by the uterine position and integrity of the Cesarean scar rather than by the number of uterine scars. The combination of a high uterine scar position and presence of a uterine scar niche act synergistically to increase the likelihood of scar/myometrial implantation in a future pregnancy.

We recently demonstrated that the uterine scar level and healing were related to the stage of labor at the time of Cesarean birth[18]. Pre-labor or early labor emergency Cesarean sections were associated with higher likelihood of a scar in the uterine cavity as well as increased incidence of a uterine niche. In contrast, a Cesarean section performed late in labor resulted in a uterine scar at or below the cervical internal os in the majority of cases with a low prevalence of uterine niches. These findings were present in a dose-dependent manner, with the highest uterine scars

occurring after elective (pre-labor) whilst the lowest cervical scars were seen after Cesareans performed at full cervical dilatation.[18] The latter observation explains the epidemiology of AIP with regards to increased risk after the second and/or elective Cesarean birth, with scar implantation being more likely when the decidual defect is in the uterus rather than in the cervical canal as seen after late labor Cesareans. The major determinant for the risk of AIP therefore appears to be timing of Cesarean birth in labor rather than the number of Cesarean births – which confers increased risk by being a proxy for the former.(Figure 1)

Strategy for reducing AIP morbdity and mortality

With the lack of an effective screening program for AIP, the rising global trend in Cesarean section rates and the strong association between a previous Cesarean birth and the subsequent development of AIP, it is inevitable that we will be faced with increasing maternal morbidity and mortality from AIP cases in the future[19–21]. An appropriate strategy for reducing maternal morbidity and mortality from AIP requires two arms – screening and prevention. Given that the strongest risk factors for AIP are previous Caesarean birth and current placenta previa, it would seem reasonable that any women presenting with these features should be referred to an AIP diagnostic service or be seen by physicians experienced in the diagnosis of AIP. Such a screening program is yet to be tested in clinical practice, but the current epidemiological evidence would suggest that it is likely to increase the rate of its antenatal diagnosis.

It is also important to consider strategies that might reduce the risk of a woman developing AIP. The strongest modifiable risk factor associated with AIP is prior elective or early labor Cesarean birth. Raising awareness of medical professionals about the consequences of Cesarean birth in general and the

importance of elective Cesarean birth in particular is vital. Promoting the importance of avoiding unnecessary operative birth to the physician is of utmost importance. It is also imperative that such information is made readily available to women thus enabling them to make informed choices that best suit their individual wishes and future plans. For a meaningful reduction in AIP prevalence, there is a need to reduce the number of pre/early labor Cesarean births performed. In this regard, stakeholders involved in this decision, with the woman herself being on the top of this list, should be made aware of the 5 fold increase in risk with caesarean birth and the imbalance in AIP risk in association with the type of caesarean where a pre/early labor cesarean is associated with a 3 fold higher risk of AIP compared to an intrapartum one.

Reducing the rate of pre/early labor Cesarean birth would require a multipronged and integrated approach that critically appraises all current indications for elective Cesarean section. Policies for trial of labor after Cesarean and external cephalic version for breech presentation should be emphasized, promoted and developed. In situations where elective Cesarean birth is unavoidable and a woman wishes to reduce her risk of subsequent AIP in a future pregnancy, consideration should be given towards replacing pre-labor Cesarean section with planned procedures to be performed when the woman presents in labor. Such a policy will have a significant impact on the position and integrity of the uterine scar and as a consequence, the woman's future risk for AIP. However this proposed policy is currently unconventional and could potentially have negative impacts on clinical, health economic and service provision outcomes. If introduced, such a policy would need to undergo thorough monitoring and auditing to assess any potential unanticipated adverse outcomes other than the inconvenience of an unscheduled

birth. Nevertheless, it is possible that it would also confer additional benefits particularly when considering the reduction of unfavorable neonatal outcomes of elective cesarean sections such as respiratory distress syndrome and transient tachypnea of the newborn.[22] Despite the balance of risks and benefits related to the process of birth itself, one has to weigh up the potential devastating consequences of an undiagnosed AIP being discovered at birth in a subsequent pregnancy.

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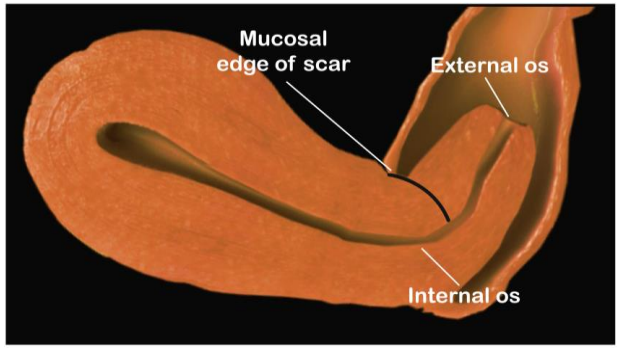
Figure legend

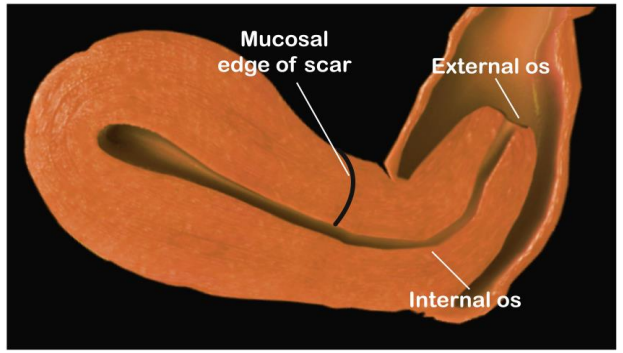
Figure 1 Sites of elective or emergency CS scar/niche and the possible evolution



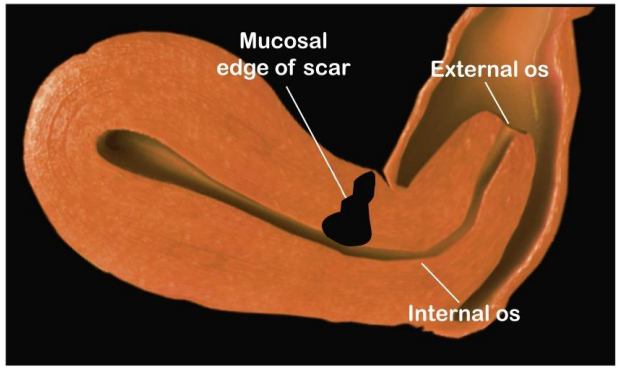
Emergency CS

NORMAL PLACENTAL INVASION

Elective CS



High scar/Niche formation



ABNORMAL INVASION OF THE PLACENTA

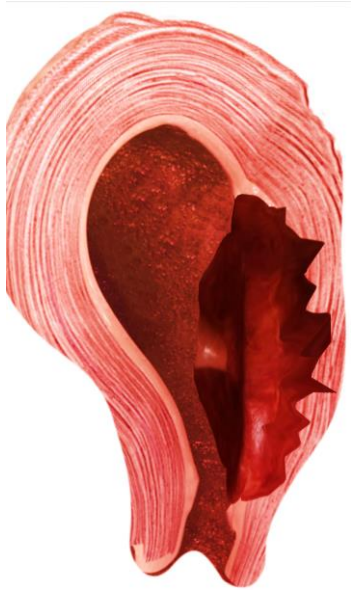


TABLE 1: Risk factors and their associated odds ratios (OR) or relative risks (RR) for abnormal invasion of the placenta (AIP) as reported in published studies.

Risk factor	**Risk for AIP**	**95% CI**
Maternal age >35yrs[8]	OR 3.13	1.4-6.97
Smoking[15]	OR 1.13	0.43-2.94
Obesity[8]	OR 1.37	1.0-1.8
Parity[8]	OR 2.50	1.7- 3.6
Previous gynecological intervention		
Laparoscopy[12]	RR 2.10	1.5-3.0
Curettage[12]	RR 2.10	1.6-2.7
IVF[8]	OR 2.80	1.2- 6.8
Hysteroscopy[12]	RR 2.90	2.2-3.8
Previous mode of birth		
Prior ELCS vs EMCS[16]	OR 3.00	1.5-6.1
Previous ≥1CS[8]	OR 4.66	3.0-7.2
Placenta location in this pregnancy		
Placenta previa[8]	OR 11.0	4.7-25.8
Placenta previa + prior CS[8]	OR 12.00	1.6- 88.0

IVF: in-vitro fertilization, CS: Cesarean section, ELCS: Elective CS; EMCS: Emergency CS