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UCL Elizabeth Garrett Anderson

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London 29th May 2020

The Editor
BP&R in Clin Ob Gyn

Dear Edwin,

Please find enclosed our manuscript entitled “**A comparison of recent guidelines in the diagnostic and management of placenta accreta spectrum disorders**” and the corresponding MCQs.

The final version has been approved by all authors who have equally contributed to the development of this project and have no conflict of interest to declare.

The length of the manuscript including the main text, references and the 2 tables is around 7000 words as required.

Very best regards

Eric Jauniaux

Highlights:

A comparison of recent guidelines in the diagnostic and management of placenta accreta spectrum disorders

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The authors report no conflict of interest.

The views expressed in this document reflect the opinion of the individuals and not necessarily those of the institutions that they represent.

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ABSTRACT (max 150 words)

1 Accreta placentation and in particular its invasive forms are impacting maternal
2
3 health outcomes globally and the prevalence of placenta accreta spectrum (PAS)
4
5 continues to increase. The Royal College of Obstetricians and Gynaecologists
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7 (RCOG) and the American College of Obstetricians and Gynecologists (ACOG) with
8
9 the Society for Maternal-Fetal Medicine (SMFM) have updated their national
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11 guidelines whereas the Federation International of Gynecology and Obstetrics
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13 (FIGO) and the Society of Obstetricians and Gynecologists of Canada (SOGC) have
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15 developed new guidelines on the diagnosis and management PAS. A comparison of
16
17 these guidelines highlights common strong recommendations on the need to
18
19 carefully evaluate women at high-risk for PAS (e.g. prior uterine surgery presenting
20
21 with anterior low-lying placenta or placenta previa), using multi-modal ultrasound
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23 imaging. For women diagnosed with PAS, multidisciplinary team-based care, with full
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25 logistic support structures (immediate access to comprehensive blood products,
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27 adult and neonatal intensive care) and established expertise in complex pelvic
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29 surgery, is critical to maximize safe outcomes for mother and newborn.
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44 **Key Words:** Placenta accreta; increta; percreta; prenatal diagnosis, risk factors,
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46 conservative management, surgical management, guidelines.
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BACKGROUND

A. Historical perspective

The first fully documented cases of birth complicated by accreta placentation were published almost one hundred years ago [1-4]. In 1937, Irving and Hertig published a cohort of 18 cases with similar clinical and pathological observations, characterized by abnormal mechanical adherence of the placenta to the underlying uterine wall, associated with severe post-partum hemorrhage (PPH), and requiring a hysterectomy in a majority of 15 cases [5]. Histologic observations noted partial or complete absence of the decidual layer which is normally present between the anchoring placental villi and the superficial myometrium. Although this series did not include a single case of placental tissue invading beyond the uterine wall, these seminal observations by Irving and Hertig remain in use today as key criteria for the diagnosis of both adherent and invasive placentation. However, they are often applied to describe the retained placenta as also being pathologically-adherent to the uterine wall [6-10]. This trend has subsequently led to increasing, and highly variable, reported rates in the overall prevalence of placenta accreta, ranging between 0.01% and 1% of livebirths [11,12].

Lukes et al. [13], in 1966 were the first group to propose a detailed histologic classification for placenta accreta based on the depth of the villous penetration of the myometrium; starting with *placenta adherenta or creta* (PC) when the villi adhere directly to the myometrium without a decidual interface. Further invasion was defined as *placenta increta* (PI) when the villi invade into the myometrium. Finally, *placenta percreta* (PP) occurs when the villi invade the full thickness of the uterine wall either to the serosa or beyond to involve extra-uterine structures, such as the bladder. They also observed that penetration of the myometrium by placental villi is rarely a

1 uniform process, such that areas of normal villi attached to decidua, adherent villi
2 attached to myometrium, and invasive villi deeper within the myometrium, may all co-
3 exist within the same specimen. To address this constellation of variable findings, a
4 majority of experts use the term “placenta accreta spectrum” (PAS). This term
5 includes all grades of abnormal placentation and is used as the basis for the
6 development of a new clinical classification proposed by the Federation International
7 of Gynecology and Obstetrics (FIGO) [14].
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17 Many clinicians and the World Health Organization (WHO) international
18 classification of diseases (www.who.int/classifications/icd) continue to use the 1937
19 Irving and Hertig definition for placenta accreta and therefore make no distinction
20 between different grades of PAS. Only 10% of studies on the prenatal diagnosis of
21 PAS and placenta previa accreta provide detailed histopathology data on the
22 different grades of PAS, and the corresponding distribution varies widely (Table 1).
23 In addition, many authors and the WHO are adding to the confusion by using a 19th
24 century “morbidly adherent placenta” terminology which refers only to abnormally
25 adherent PAS. This has led to many authors to over-diagnose the incidence of PAS
26 by including cases which present as complete or partial placental retention, or with
27 excessive bleeding from the placental bed at Cesarean delivery [6,8,10].
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43 Furthermore, in women delivered by repeat Cesarean, there may be a tendency to
44 over-diagnose PAS in circumstances where the low-lying anterior placenta is visible
45 through the old thin scar region due to lower-segment dehiscence. This scar may
46 expand during pregnancy to create a large uterine “window” through which a portion
47 of the placenta is visible - without any villous tissue truly invading the serosa and/or
48 the surrounding myometrium [15].
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A new standardised classification and reporting guidelines for the pathology diagnosis of PAS has also been recently proposed by an expert panel [16]. This new classification, together with the 2016 standardized ultrasound and MRI descriptions and proforma reporting for suspected antenatally with placenta accreta, [17-19] have been established with the intent of improving the overall quality of epidemiologic data on PAS incidence. This system also may improve management outcome data, by allowing stratification using the standardized different grades of PAS.

B. Epidemiology

Until the 1950s, the predisposing factors for PAS in subsequent pregnancies were manual removal of the placenta, endometritis and/or “vigorous” uterine curettage during a prior delivery [5]. Today, over 95% of women diagnosed prenatally with PAS present with a low-lying/placenta previa and a surgical history of at least one prior uterine surgery, most commonly Cesarean delivery (CD) [20-22]. The rapid increase in CD rates around the world, together with a greater prevalence of prior gynecologic surgery (myomectomy, uterine adhesiolysis, septal resection), means that up to 6% of the pregnant population have the combination of a low-lying anterior placenta and prior uterine surgery, at their 12-week nuchal translucency ultrasound examination (Panaitova et al., USOG 2018). Advanced reproductive age at conception and use of in-vitro fertilization methods have also contributed to the increased incidence of placenta previa. For example, there is strong epidemiologic evidence that the incidence of placenta previa accreta increases with the number of prior CDs (22-24). The ratio of adherent/invasive accreta placentas has changed from 7/3 in the 1970s to 5/5 in the last two decades [22], a change that is directly linked to the increase in the number of grand multiparas with multiple CD scars undertaking further

1 pregnancies [25,26]. Pregnancy following multiple CDs is also a major risk factor for
2 large cesarean scar defects (CSD), and for the development of cesarean scar
3 pregnancies (CSP) in the cervico-isthmic niche created by focal myometrial loss at
4 the site of prior CDs [27]. The diagnosis of CSP in the first trimester is increasingly
5 common, such that the natural history of evolution to PAS has now been clearly
6 established, especially for type-2 CSP. Since CSPs may lead to early uterine rupture
7 and emergency hysterectomy [28], or more increasingly, be managed immediately
8 by medical, or laparoscopic surgery methods (PMID 28601471), their diagnosis and
9 management will further alter the epidemiology of PAS at birth.
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21 PAS is not exclusively a consequence of CD and has been reported in
22 primiparous women with a history of operative hysteroscopy, suction curettage,
23 surgical termination, endometrial ablation, uterine pathology such as bicornuate
24 uterus, adhesiolysis for Asherman's syndrome, adenomyosis, endometrial resection,
25 polyvinyl bead embolization of fibroids, and myotonic dystrophy [22,25,29]. In fact,
26 any procedure causing surgical or substantial and chronic damage to the integrity of
27 the uterine wall, especially if the endometrium fails to re-epithelize in an area of scar
28 formation, has been associated with PAS [25,26]. Accreta placentation can occur
29 after myomectomy but the risk is low [30] unless the uterine cavity is entered,
30 because the endoscopic removal of intramural or sub-serous fibroids does not
31 involve the uterine cavity [31]. Though the removal of fibroids in the upper part of the
32 uterus is less likely to lead to uterine dehiscence [32], focal PAS may still occur.
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34 Undoubtedly PAS has increased as a consequence of modern obstetric and
35 reproductive medical practices, and has been accentuated by decisions to delay
36 childbearing, the need for subsequent reproductive assistance and the prevalence of
37 prior gynecologic surgery [25].
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C. The “World No 1” surgical procedure effect

Safe Caesarean delivery (CD) is an essential component of a secure, functioning and comprehensive maternity system, and is now the most commonly performed major operation around the world, with more than 1 million procedures performed each year in the USA alone [33]. In 1985, a group of experts advising the WHO highlighted an unjustified and remarkable increase in CD rates worldwide in the prior decade [34]. They stated there was no justification for any country or region to have a caesarean section rate higher than 10–15%. This recommendation has had little impact on the rates of CD in most countries of the world, which have continued to rise over the following four decades [35]. In 2011, Solheim et al., published a decision-analytic model using data on national birthing order trends after CD rates in the U.S. between 1995 and 2005. They estimated that if the number of primary and secondary CDs continue to rise, by 2020 the CD rate will be 56.2%, and that as a consequence there will be an additional 6236 placenta praevias, 4504 PAS, and 130 maternal deaths annually [36]. The CD rates have not risen to this level in the U.S. but have risen above 40% over the past decade in many middle-income countries around the world with mixed public-private health care systems, such as Brazil, Turkey, Italy, Egypt, Argentina, Iran, South Korea and Mexico. Solheim et al., calculated that the rise in CD-associated complications will lag behind the rise in CDs by around 6 years [36]. These data highlight the need for local health providers to become prepared for a significant rise in the numbers of pregnancies complicated by placenta previa accreta. In particular, in middle-income countries with high-birth rates such as Turkey and Egypt, where more than half of all births are via CD, the

1 prevalence and negative impacts of PAS have now outweighed the benefits of
2 improved access to quality obstetric care at the population-based level.
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5 The 2017 report from the UK and Ireland Confidential Enquiries into Maternal
6 Deaths indicated that although there was no significant change in the maternal death
7 rate in the UK between 2010–12 and 2013–15, an increase in the number of deaths
8 associated with PAS was observed [37]. Not surprisingly, as PAS has become a
9 new risk factor for major obstetric complications, there has been an exponential
10 increase in the number of articles published in the medical literature over the last
11 decade. In an editorial for the special issue of the International Journal in
12 Gynecology and Obstetrics we reported that a PubMed
13 (www.ncbi.nlm.nih.gov/pubmed) search of the term “placenta accreta” up to 1st of
14 December 2017 generated 2296 hits [20]. Through the 1st of May 2020, there have
15 been another 569 new articles published. Each year since 2010, more publications
16 on placenta accreta have occurred than during the entire period between 1947-1962.
17 These new data have stimulated the development of new national and international
18 guidelines and the updating of previous guidelines. These guidelines have extracted,
19 analyzed and summarized recent quality evidence-based data on diagnosis and
20 management of PAS. They are therefore essential to inform local and international
21 policies and health provision for the development of maternity centres with specialist
22 surgeons, equipment, drugs, blood bank and intensive care infrastructure to safely
23 manage the new epidemic of women presenting with PAS.
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53 **CLINICAL GUIDELINES FOR DIAGNOSIS AND MAGEMENT OF PAS**

54 ***A. New and updated guidelines***

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There are currently two recently updated and two new guidelines on the diagnosis and management of PAS available in the recent international medical literature:

- The 2018 Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 27a which includes both placenta praevia and placenta accreta and has replaced the 2011 edition of the guidelines Placenta Praevia, Placenta Praevia Accreta and Vasa Praevia: Diagnosis and Management. This is the 4th edition of this guidelines and the first to be published in the British Journal of Obstetrics and Gynaecology [38]. The first edition, published in 2001, was entitled Placenta Praevia: Diagnosis and thus did not include placenta accreta.
- The 2018 American College of Obstetricians and Gynecologists (ACOG) obstetric care consensus was developed jointly with the Society for Maternal-Fetal Medicine (SMFM) and endorsed by the Society of Gynecologic Oncology (SGO) and replaced the Committee Opinion No. 529, of July 2012 and SMFM Clinical Guideline of November 2010. These guidelines were published simultaneously in Obstetrics and Gynecology [39], the official journal of ACOG and the American Journal of Obstetrics and Gynecology (40).
- The 2018 FIGO consensus guidelines on placenta accreta spectrum disorders were developed by the Safe Motherhood and Newborn Health Committee [41]. The guidelines are presented in four separated expert reviews: Epidemiology [22], prenatal diagnosis and screening [42], non-conservative surgical management [43] and conservative management [44] and were published simultaneously on the FIGO website and a special issue of the

1 International Journal of Gynaecology and Obstetrics, the official journal of the
2 FIGO.
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5 - The 2019 Society of Obstetricians and Gynecologists of Canada (SOGC) No.
6 383-screening, diagnosis, and management of placenta accreta spectrum
7 disorders [45] which was published simultaneously in English and French in
8 the Journal of Obstetrics and Gynaecology of Canada, the official journal of
9 the SOGC.
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17 18 19 ***B. Development process*** 20

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22 - The RCOG guidelines are developed by stakeholders representing health care
23 in the UK from the best research evidence. They are recommendations for
24 good practice that are not meant to dictate care, but rather to support
25 healthcare professionals in their work; some recommendations may not be
26 transferable to non-UK settings. The guideline authors included a lead
27 developer and a team of local and international multidisciplinary group of
28 experts who assessed the evidence gathered in a systematic matter. The
29 authors evaluated the methodology of each study and graded the evidence
30 from level 1 to level 4 depending on its individual value for the guidelines. The
31 guideline authors drew up recommendations for each point, which are graded
32 A, B, C and “good practice” according to the strength of the evidence that
33 supports them (Table 2). The draft guideline document then went through a
34 process of consultation and peer-review and the final version was approved
35 by the Guidelines Committee and the RCOG Clinical Quality Board. In
36 addition to the guidelines, the RCOG produced an information leaflet for the
37 public.
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1 - The ACOG and SMFM guidelines are developed in a fashion quite similar to
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3 the RCOG document. They are also considered recommendations or
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5 guidelines, with the recognition that not all clinicians and settings have
6
7 equivalent resources. The guideline authors included a lead developer and a
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9 national team of maternal-fetal-medicine based experts with representation
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11 from both societies. The authors were provided a compilation of available
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13 studies and data that were gathered in a systematic matter. The authors
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15 evaluated the methodology of each study and used them to make
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17 recommendations. Recommendations were given as strong (1), weak (2), or
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19 best practices (in the absence of evidence). In addition, the quality of
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21 evidence was graded as A (high), B (moderate) and C (low) (Table 3). The
22
23 draft guideline document then went through a process of consultation and
24
25 peer-review and the final version was approved by the ACOG Obstetric
26
27 Guidelines Committee and the SMFM publications committee.

28 - The FIGO guidelines: were developed as expert evidence-based opinions
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30 with the aim of helping clinicians, policymakers, and patients to make well-
31
32 considered decisions about health care for a particular condition. The
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34 guidelines were intended to be transferable to an international setting and
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36 were therefore based on consensus from a group of international specialists
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38 who were individually proposed for their expertise by their national
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40 professional societies of obstetricians and gynaecologists. The guidelines
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42 provided clear, well-reasoned information such that decision makers can use
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44 them effectively both nationally and globally. The quality of evidence was
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46 graded as high, medium or low according to the methodology of the studies
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1 reviewed. The guideline authors drew up recommendations which were
2 graded as strong or weak and combined these into a table with the quality of
3 evidence. The final version was approved by the FIGO Safe Motherhood and
4 Newborn Health Committee.
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12 - The SOGC guidelines: were developed by the multidisciplinary team
13 members based at the largest site providing care for women with PAS in
14 Canada with prior approval by the national society SOGC. The final guideline
15 was approved by both the maternal-fetal medicine and the diagnostic imaging
16 guideline committees using the established evidence-based grading systems
17 used for all SOGC national clinical practice guidelines. Broad consensus was
18 achieved across Canada as reflected by the final author listing. Members from
19 this guideline also contributed to the FIGO guidelines.
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32 **COMPARISON OF THE RCOG, ACOG/SMFM, FIGO AND SOGC GUIDELINES**

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36 The classification of evidence levels and recommendations provided by the different
37 guidelines is directly linked to the quality of the data available in studies published at
38 the time of the development of the corresponding guidelines. The recommendations
39 therefore changed to some extent with time, as is illustrated by the RCOG and
40 ACOG/SMFM guidelines, which are now in their 3rd editions. In the case of PAS,
41 most of the cohort studies published before 2015 are retrospective and thus lack the
42 more accurate modern clinical descriptions and detailed histopathologic
43 examinations required to confirm the diagnosis of the different grades of PAS, and
44 therefore their specific management recommendations. Recent systematic reviews
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1 and meta-analyses on the overall prevalence of PAS and the incidence of placenta
2 previa accreta show large amounts of heterogeneity between population studies for
3 the prevalence, incidence and distribution of the different grades PAS, as well as
4 rates of peripartum hysterectomy, haemorrhage requiring transfusions and maternal
5 mortality. These wide variations between studies are due to inconsistency with
6 regards to the criteria used to diagnose and confirm the nature of PAS at birth
7 [12,21]. Surprisingly there is also high heterogeneity in qualitative and diagnostic
8 data on the ultrasound criteria used in cohort studies, reporting on placenta previa
9 accreta, for the much simpler ultrasound diagnosis of placenta previa and the
10 gestational at confirmation of the diagnosis [21].
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26 ***A. On prenatal diagnosis***

27 A 2017-2018 international survey of practices used in the diagnosis and
28 management of PAS disorders found that 92% of respondents indicated that their
29 department routinely performs prenatal screening of women identified as being at
30 high risk of PAS disorder [46]. Of those, a similar % reported that such screening
31 was prompted by a prior history of uterine surgery and/or cesarean delivery plus a
32 low-lying placenta or placenta previa at mid-pregnancy using grey-scale
33 transabdominal ultrasonography. The most common additional method of diagnosis
34 among women with a high suspicion for PAS disorders was transvaginal sonography
35 (TVS) and over 61% use both ultrasonography and magnetic resonance imaging
36 (MRI).
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52 All the guidelines agree that:

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- 1 ▪ Ultrasonography is a relatively inexpensive and widely available imaging
2 modality and therefore should be the first line for the diagnosis of PAS.
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- 4 ▪ Previous CD and the presence of an anterior low-lying/placenta praevia
5 should alert the antenatal care team of the higher risk of PAS.
6
- 7 ▪ MRI is not essential for making a prenatal diagnosis of suspected PAS and is
8 therefore not the preferred primary imaging modality for the initial evaluation
9 of women at risk of PAS.
10

11 The RCOG guidelines identify ultrasound imaging as highly accurate (> 95%) when
12 performed by a skilled operator with experience in diagnosing PAS (Grade C) and
13 the ACOG/SMFM highlights that although ultrasound evaluation is important, the
14 absence of ultrasound findings does not preclude a diagnosis of PAS and that
15 clinical risk factors remain equally important as predictors of PAS by ultrasound
16 findings (Grade 1A). In addition, the SOGC states that the effectiveness of
17 ultrasound in the context of PAS depends upon awareness of clinical risk factors,
18 imaging quality, operator experience, gestational age, imaging modalities, and
19 adequate bladder filling. The FIGO strongly recommends that the ultrasound signs of
20 PAS should be described using standardised protocols. On the basis of at least one
21 systematic review and meta-analysis, the RCOG guidelines recommend referral of
22 women with any ultrasound features suggestive of PAS to a specialist unit with
23 imaging expertise (Grade B). The ACOG/SMFM suggest performance of ultrasound
24 examinations at approximately 18-20, 28-30, and 32-34 weeks of gestation
25 in asymptomatic patients. The RCOG indicates that TVS has an important role in
26 the early diagnosis, follow-up, differential diagnosis between adherent and invasive
27 accreta placentation and overall management of PAS [*Evidence level 4*].
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29 For the RCOG, FIGO and SOGC, MRI may be useful in evaluating the pelvic
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1 extension of a placenta percreta or areas difficult to evaluate on ultrasound, though
2 its effectiveness is currently limited by the relative contraindication to the use of a
3 gadolinium contrast enhancing agent. For ACOG it is unclear whether MRI improves
4 diagnosis of PAS beyond that achieved with ultrasonography alone. On the basis of
5 two systematic reviews and meta-analyses, the RCOG concluded that the diagnostic
6 value of ultrasound imaging and MRI in detecting PAS is similar (Grade C).
7 Furthermore, the focus and experience of the supervising/reporting radiologist
8 remains an important and less well-studied factor in the diagnostic accuracy of MRI,
9 since access to expert radiologists with a special interest in pregnancy is highly
10 variable between centers.
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27 ***B. On preparing for delivery***

28 A recent anonymous survey of the 154 obstetrical services in NHS England found
29 that of the 114 that responded, 70% manage their PAS cases "in-house", despite
30 one third of these units reporting that they manage on average only one case per
31 year [47]. The 23 units that describe themselves as "specialist centres" managed a
32 median of four cases per year. There is mounting evidence from before and after the
33 publications of the new guidelines that women with PAS diagnosed prenatally and
34 managed by a multidisciplinary team (MDT) in a centre of excellence (CoE) are less
35 likely to require emergency surgery, large-volume blood transfusion and reoperation
36 within 7 days of delivery for bleeding complications compared with women managed
37 by standard obstetric care without a specific protocol [48]. Although, there is no
38 evidence for an ideal minimal number of cases of PAS managed per month or year,
39 maternal outcomes are improved over time with increasing experience within a well-
40 established MDT performing 2–3 cases per month [49,50].
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There are also wide variations between healthcare providers within the U.S. [51,52] and between different countries [46,53] in the preparation for the surgical procedure such as the use of cystoscopy and placement of ureteral stents, the involvement of different surgical specialities in the operating team, the choice of anaesthesia technique and the use of additional techniques such as interventional radiology (IR) pre-operative placement of an arterial balloon either in the lower aorta, common iliac or anterior divisions of the internal iliac arteries.

All the guidelines recommend that:

- Patients diagnosed with PAS should be cared for by a MDT with expertise in complex pelvic surgery in a specialist centre with logistic support for immediate access to blood products, adult and neonatal intensive care.
- Preoperative coordination with protocol-based interdisciplinary care including anaesthesiology, hematology/blood bank, maternal-fetal medicine, neonatology, and expert pelvic surgeons to optimize intraoperative and post-operative outcomes.
- Preoperative counselling should include review of planned and possible alternate surgical strategies and complications and that a contingency plan for emergency delivery should be developed, including the use of an institutional protocol for the management of maternal haemorrhage.

All the guidelines agree that:

- Use of antenatal corticosteroids for lung maturation by 32-34 weeks is appropriate in women with antenatally diagnosed PAS and with current

1 national and international gestational age-based recommendations for
2 anticipated delivery before term.
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- 4
5 ■ No amniocentesis is necessary because data regarding pulmonary maturity
6 do not change clinical recommendations for emergency delivery before 36
7 weeks.
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10 ■ There are currently insufficient data to recommend the routine use of
11 cystoscopic assessment of the bladder and placement of ureteric stents but
12 collaboration with a urologic surgeon is advisable in cases with suspected
13 bladder wall involvement.
14
- 15 ■ Optimizing hemoglobin values during pregnancy is important and when iron
16 deficiency is noted oral replacement or intravenous infusions should be
17 implemented and when available intraoperative cell salvage may be utilized or
18 be on “stand-by”.
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- 20 ■ Timing of delivery decisions need to balance maternal risks and benefits with
21 those of the fetus or neonate.
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37 The guidelines give different opinions for the optimal timing for delivery. For the
38 ACOG/SMFM between 34⁺⁰ and 35⁺⁶ weeks of gestation is the recommended
39 gestational age for scheduled cesarean delivery or hysterectomy absent extenuating
40 circumstances in a stable patient (1A) whereas for the RCOG, in the absence of risk
41 factors for preterm delivery and/or bleeding from a placenta previa, indicate that
42 planned delivery at 35⁺⁰-36⁺⁶ weeks of gestation provides the best balance between
43 fetal maturity and the risk of unscheduled delivery [GPP]. The SOGC recommends
44 that for otherwise healthy women with no history of vaginal bleeding, the optimal
45 timing of elective CD is around 34–36 weeks of gestation (II-3B). FIGO guidelines
46 are based on consensus from expert from high-, medium- and low-resources
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1 countries. Low resource countries, in particular in Africa have often limited or no
2 access to blood products and ICU and thus the FIGO does not formally recommend
3 a preferred time for delivery as for low resources countries moving the delivery date
4 as close as possible to 37 weeks has a direct impact in reducing poor neonatal
5 outcome.
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11 A survey of 26 Israeli hospital maternities reported that general anesthesia was
12 used almost exclusively among women with high suspicion for PAS disorders [53].
13 The international survey of FIGO experts found that spinal–epidural anesthesia was
14 used by 44% of the respondents [46]. The RCOG recommends that the choice of
15 anaesthesia technique should be should be made by the anaesthetist conducting the
16 procedure in consultation with the patient in advance [GPP] whereas for the SOGC,
17 regional epidural anaesthesia is considered safer than general anaesthesia in most
18 instances, is associated with reduced blood loss, is preferred by patients and their
19 partners and affords a 24-hour window of effective post-operative pain relief (II-2A).
20 The RCOG also recommend that the patient should be informed that the surgical
21 procedure can be performed safely with regional anaesthesia but should be advised
22 that it may be necessary to convert to general anaesthesia if required and asked to
23 consent [D]. The ACOG/SMFM does not comment on this issue and the FIGO
24 guidelines highlight that there is insufficient evidence to support the use of one
25 technique over the other.
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51 **C. On management**

52 Overall four management approaches have been described alone or in combination
53 with additional procedures mainly iliac or uterine artery devascularisation techniques,
54 either surgical or using interventional radiology (IR).
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The radical techniques are:

- Primary hysterectomy (PH) following immediately the delivery of the infant, without attempting placental separation.
- Delayed or secondary hysterectomy between 3 days and 12 weeks after delivery of the infant, leaving the placenta in situ, with repair of the hysterotomy incision.

The conservative techniques are:

- Leaving partially or totally the placenta in situ after delivery of the infant, avoiding the placenta, with repair of the hysterotomy incision (expectant management).
- Partial myometrial resection (partial excision of the accreta area) following the delivery of the infant, and without disturbing the placenta, followed by repair of the uterus.

Planned preterm caesarean hysterectomy with the placenta left *in situ* has been the recommended management strategy for PAS by both RCOG and ACOG/SMFM in the previous version of their guidelines. Not surprisingly, surveys of healthcare providers in the U.S. published in 2012 [51] and 2013 [52] found that most ACOG fellows SMFM members proceeded with hysterectomy and only 14.9%–32.0% reported attempting conservative management. The 2018 international survey reported that around 60% of the respondents favored a radical surgical management approach with cesarean hysterectomy i.e. primary cesarean hysterectomy with the placenta left in situ, whereas 10 (28%) would perform a partial myometrial resection or radical dissection whenever possible [46]. Primary attempt at placental removal and compression sutures were attempted by a quarter of experts and around half of the respondents used intra-arterial balloons or arterial embolization [46].

1
2 All the guidelines recommend that:
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- 4 ▪ The delivery hysterotomy should be performed high without incising through
5 the placenta.
6
- 7 ▪ No attempt should be made to remove the placenta (extirpative approach or
8 forcible manual removal of the placenta) if it shows no signs of separation as
9 this may cause substantial hemorrhage.
10
- 11 ▪ If at the time of an elective repeat caesarean section, PAS is suspected based
12 on uterine appearance and there are no extenuating circumstances
13 mandating immediate delivery, the caesarean section should be delayed until
14 until optimal surgical expertise arrives and adequate blood products are
15 available.
16
- 17 ▪ Conservative management or expectant management should be considered
18 only for carefully selected cases of PAS after detailed counseling about the
19 risks, uncertain benefits, and efficacy and local arrangements need to be
20 made to ensure regular review, ultrasound examination and access to
21 emergency care should the patient experience complications.
22
- 23 ▪ Uterus-preserving surgical techniques should only be attempted by surgeons
24 working in teams with appropriate expertise to manage such cases.
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- 26 ▪ MTX adjuvant therapy should not be used for expectant management as it is
27 of unproven benefit and has significant adverse effects, including maternal
28 mortality.
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55 All the guidelines agree that:
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- There is insufficient evidence to recommend giving or withholding uterotonic drugs after delivery of the fetus
- There is insufficient evidence to recommend routine IR techniques such as embolisation or placement of an arterial segment balloon designed to arrest arterial blood flow that may supply the gravid uterus.

The RCOG guidelines indicate that when the extent of the placenta accreta is limited in depth and surface area, and the entire placental implantation area is accessible and visualised (i.e. completely anterior, fundal or posterior without deep pelvic invasion), uterus-preserving surgery may be appropriate, including partial myometrial resection. [GPP]. The ACOG/SMFM guidelines highlight that because of a lack of comparative data, choice of skin incision is left to operator judgment, although many employ vertical incisions for better access and visualization whereas both the FIGO and SOGC guidelines recommend midline skin incision sufficiently high to allow a hysterotomy above the superior placental margin in high-suspicion PAS with major anterior previa. The ACOG/SMFM and FIGO guidelines indicate that in most cases when hysterectomy is necessary, a total hysterectomy is required because lower uterine segment or cervical bleeding due to cervical involvement frequently precludes a supra-cervical (partial) hysterectomy, Total hysterectomy also reduces the potential risk of malignancy developing in the cervical stump, the need for regular cervical cytology and other associated problems such as bleeding or discharge.

UNRESOLVED ISSUES

1 All authors and experts involved in developing the different guidelines noted that
2 most current information on both prenatal diagnosis and management is derived
3 from retrospective cohort studies without controls, case series and expert opinion.
4
5 A search of PubMed using the MeSH headings for “placenta accreta, placenta
6 increta, placenta percreta, abnormally invasive placenta and morbidly adherent
7 placenta” published between May 2019 and May 2020 found 189 articles including
8 122 retrospective and two prospective cohort studies, 30 cases reports, 22 expert
9 opinions, 7 case series, five systematic review and meta-analyses and only one RCT
10 [54]. Furthermore, the absence of detailed histopathological evidence and lack of
11 standardized clinical or photographic evidence of PAS at birth in around 90% of
12 cohort studies [11,12] considerably limits the value of the corresponding data and
13 make it is impossible to reproduce such results in other centers or populations, or
14 carry out meaningful meta-analysis. This highlights the difficulties of finding high
15 quality evidence to support strong recommendations.
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34 There are some generally agreed upon strategies, but comparison of the
35 different guidelines shows (Table 5), that even those recommendations graded as
36 strong, in particular regarding management, are not supported by well-performed
37 RCTs. Interestingly, both the FIGO and SOGC strongly recommend the use of
38 tranexamic acid during surgery for PAS but there are no cohort series available in
39 the literature and only one small RCTs in cases of (non-accreta) placenta previa
40 combining bilateral uterine artery ligation with tranexamic acid [55].
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51 The pivotal role of ultrasound imaging in the screening women at risk and in
52 accurately diagnosing PAS prenatally is highlighted in all guidelines. However, the
53 ACOG/SMFM guidelines indicate that the standardized description of
54 ultrasonography features of PAS [17] and *pro forma* for standardized reporting of
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1 ultrasound [18] proposed by an international group of imaging experts are not yet in
2 widespread use in the U.S. and there is no evidence that they are routinely used in
3
4 many other countries. The diagnosis of PAS is not part of general ultrasound training
5
6 courses in the U.K [56] and it has only been added to the fetal medicine foundation
7
8 website earlier this year ([www//coursesf.etalmedicine.com](http://www/coursesfetalmedicine.com)). However, such
9
10 ultrasound training and screening programs have existed for more than two decades
11
12 for the detection of fetal anomalies such as congenital heart defect. Surprisingly, as
13
14 this was one of the first objective of the use of ultrasound in obstetrics, the criteria
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16 used by authors of cohort series and gestational age at confirmation diagnosis of
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18 placenta previa remains highly variable [12]. Considering the increasing incidence of
19
20 placenta previa accreta around the world and the high maternal morbidity and
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22 mortality at delivery of undiagnosed cases, similar international screening protocols
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24 with standard anatomical views for both low-lying/placenta previa and PAS should be
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26 implemented.
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42 **Conflicts of interest**

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45 The authors have no conflicts of interest.
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SUMMARY (max 250 words)

1
2 The changes in the epidemiology of placenta previa and placenta accreta spectrum
3
4 (PAS) have been closely linked to the rapid rise in caesarean delivery (CD) rates
5
6 over the last three decades. From a rare pathologic condition, PAS has become a
7
8 new risk factor for major obstetric complications. The changes in the prevalence of
9
10 PAS lag behind the rise in CDs by around 6 years and health providers must prepare
11
12 for a significant rise in the numbers of pregnancies complicated by placenta previa
13
14 accreta. New national and international guidelines or the update of existing ones for
15
16 the diagnosis and management of PAS have highlighted the importance of the early
17
18 identification of women with the condition. This is especially true for those
19
20 presenting with an anterior low-lying/placenta praevia and one or more prior CD
21
22 since they are at the highest risk of PAS. The crucial role of ultrasound imaging for
23
24 the antenatal screening and diagnosis, the need for women diagnosed with PAS to
25
26 be cared for by a multidisciplinary team and the importance of avoiding the placenta
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28 during the hysterotomy and/or attempt to remove it when PAS is suspected at
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30 delivery are key to reducing morbidity. Most current information on both prenatal
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32 diagnosis and management is derived from uncontrolled retrospective cohort studies
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34 and case series; in around 90% of cases there is no detailed histopathological
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36 evidence to confirm the severity of the PAS encountered. All guidelines agree on the
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38 need for new prospective controlled cohort studies and randomized controlled trials
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40 to compare the efficacy of the different therapeutic approaches and the use
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42 additional management techniques.
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PRACTICE POINTS

- Women presenting with low-lying/placenta previa and a history of one or more CDs should be carefully assessed for PAS.
- The diagnosis of PAS should be confirmed by trained operators in ultrasound imaging and regular follow-up should be arranged until delivery.
- MRI is not essential for the diagnosis of PAS and its use is limited by cost and the availability of radiology experts in the evaluation of PAS
- Delivery should be planned and managed by an MDT with regular established expertise in complex uterine surgery and access to blood products and adult and neonatal ICUs.
- The optimal time of delivery is guided by maternal symptoms associated with placenta previa and must balance the risks and advantages for mother and baby which may be different in low- median- and high-income countries.

RESEARCH AGENDA

Health provision for the development of MDT with specialist surgeons, equipment, drugs, blood bank and intensive care infrastructure to safely manage women presenting with PAS requires an accurate evaluation of its prevalence and outcome which entails the use of standardized antenatal and post-natal diagnostic protocols. Within this context, there is a need for prospective multi-centre studies with participatory methodologies involving local service providers and management adapted to the grade of PAS and local facilities. There is also a need to evaluate the health and economic consequences of high caesarean section rates on maternal health within particular population context.

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Table 1: Summary of epidemiology data and distribution of PAS grades in population studies [11] and studies of placenta previa accreta [12] diagnosed antenatally.

	Population	Placenta previa accreta
No of articles included in study	29	20
Retrospective/Prospective	22/7	13/7
No of cases of PAS/births & pregnancies (Prevalence)	7,001/5,719,992 (0.12%) 1/817	587/1,231,160 (0.05%) 1/2,097
No of PAS cases with detailed histopathology/total No of cases in study (%)	770/832 (92.5%)	283/309 (91.6%)
Placenta creta/adherenta	473 (61.4%) Range 34.8-81.6%	171 (60.4%) Range 30.4-92.3%
Placenta increta	126 (16.4%) Range 3.7-43.5%	74 (26.2%) Range 0-45.7%
Placenta percreta	171 (22.2%) Range 6.6-51.9%	38 (13.4%) Range 2.4-35.3%

PAS= Placenta Accreta Spectrum

Table 2. RCOG

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1-	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
Good Practice Points (GPP) Recommended best practice based on the clinical experience of the guideline development group	

Table 3. ACOC/SMFM

Grading of recommendations assessment	Quality of supporting evidence
1A. Strong recommendation, high-quality evidence	Consistent evidence from well performed RCTs or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.
1B. Strong recommendation, moderate-quality evidence	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
1C. Strong recommendation, low-quality evidence	Evidence from observational studies, unsystematic clinical experience, or from RCTs with serious flaws. Any estimate of effect is uncertain.
2A. Weak recommendation, high-quality evidence	Consistent evidence from well performed RCTs or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.
2B. Weak recommendation, moderate-quality evidence	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.
2C. Weak recommendation, low-quality evidence	Evidence from observational studies, unsystematic clinical experience, or from RCTs with serious flaws. Any estimate of effect is uncertain.
Best practice	Recommendation in which either (i) there is enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize), or (ii) recommendation to contrary would be unethical.

RCT= randomized controlled trial.

Table 4. SOGC Key to evidence statements and grading of recommendations

Quality of evidence assessment	Classification of recommendations
I: Evidence obtained from at least one properly RCT.	A. There is good evidence to recommend the clinical preventive action.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to recommend the clinical preventive action.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making.
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action. E. There is good evidence to recommend against the clinical preventive action.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision making.

RCT= randomized controlled trial.

PRACTICE POINTS

- Women presenting with low-lying/placenta previa and a history of one or more CDs should be carefully assessed for PAS.
- The diagnosis of PAS should be confirmed by trained operators in ultrasound imaging and regular follow-up should be arranged until delivery.
- MRI is not essential for the diagnosis of PAS and its use is limited by cost and the availability of radiology experts in the evaluation of PAS
- Delivery should be planned and managed by an MDT with regular established expertise in complex uterine surgery and access to blood products and adult and neonatal ICUs.
- The optimal time of delivery is guided by maternal symptoms associated with placenta previa and must balance the risks and advantages for mother and baby which may be different in low- median- and high-income countries.

RESEARCH AGENDA

Health provision for the development of MDT with specialist surgeons, equipment, drugs, blood bank and intensive care infrastructure to safely manage women presenting with PAS requires an accurate evaluation of its prevalence and outcome which entails the use of standardized antenatal and post-natal diagnostic protocols. Within this context, there is a need for prospective multi-centre studies with participatory methodologies involving local service providers and management adapted to the grade of PAS and local facilities. There is also a need to evaluate the health and economic consequences of high caesarean section rates on maternal health within particular population context.

MCQs for the manuscript: A comparison of recent guidelines in the diagnostic and management of placenta accreta spectrum disorders

1. The following is true about the epidemiology of PAS:
 - a. Less than 30% of women diagnosed prenatally with PAS present with a low-lying/placenta previa and a surgical history of at least one prior uterine surgery, most commonly cesarean delivery (CD).
 - b. The incidence of placenta previa accreta increases with the number of prior CDs.
 - c. Prior gynecologic surgery (myomectomy, uterine adhesiolysis, septal resection) and some uterine pathology such as bicornuate uterus have not been associated with the development of PAS in subsequent pregnancies.
 - d. Large cesarean scar defects (CSD) can lead to the development of cesarean scar pregnancies (CSP) which can be a precursor for the development of PAS

a= F; b= T; c= F; d= T

Explanation to the answers for Question 1:

- a. CD rates have risen worldwide over the last decades sometime above 40% in countries such as Brazil, Turkey, Italy, Egypt, Argentina, Iran, South Korea and Mexico. As CD scar increase the risk of both previa and accreta placentation Today, over 95% of women diagnosed prenatally with PAS present with a low-lying/placenta previa and a surgical history of at least one prior CD.
- b. Multiple CDs create substantial and chronic damage to the integrity of the uterine wall, especially if the endometrium fails to re-epithelize in an area of scar formation facilitating the development of PAS.
- c. Accreta placentation has been described after most minor gynaecologic surgical procedure including myomectomy but the risk is low unless the uterine cavity is entered or the myometrium is perforated.
- d. The diagnosis of CSP in the first trimester is increasingly common, such that the natural history of evolution to PAS has now been clearly established, especially for type-2 CSP.

2. On the prenatal diagnosis of PAS the RCOG, ACOG/SMFM, FIGO & SOGC agree that:
- a. Antenatal diagnosis of PAS is crucial in planning its management and has been shown to reduce maternal morbidity and mortality.
 - b. Previous uterine curettages and the presence of an anterior low-lying/placenta praevia should alert the antenatal care team of the higher risk of PAS.
 - c. Ultrasonography is a relatively inexpensive and widely available imaging modality and therefore should be the first line for the diagnosis of PAS.
 - d. MRI is essential for making a prenatal diagnosis of suspected PAS and should be performed in all cases of women at risk of PAS.

a =T; b= F; c= T; d= F

Explanation to the answers for Question 2:

- a. There is mounting evidence that women with PAS diagnosed prenatally and managed by a multidisciplinary team (MDT) in a centre of excellence (CoE) are less likely to require emergency surgery, large-volume blood transfusion and reoperation within 7 days of delivery for bleeding complications compared with women managed by standard obstetric care without a specific protocol.
- b. Uterine curettage in particular if complicated with uterine perforation usually damage the myometrium above the lower segment. These can be associated with focal PAS of the anterior uterine wall or fundus but the patients with the highest risk of PAS are those with prior multiple CDs presenting with an anterior low-lying/placenta praevia.
- c. Ultrasound is operator dependent and until recently there was no training available for the ultrasound diagnosis of PAS but in expert hands it has a positive predictive value, negative predictive value and detection rate above 95%. The diagnosis of PAS is not part of general ultrasound training courses in the U.K and it has only been added to the fetal medicine foundation website earlier this year (www.coursesfetalmedicine.com).
- d. MRI may be useful in evaluating the pelvic extension of a placenta percreta or areas difficult to evaluate on ultrasound, but not essential and its effectiveness is currently limited by the relative contraindication to the use of a gadolinium contrast enhancing agent.

3. On preparation for delivery and management of PAS the RCOG, ACOG/SMFM, FIGO & SOGC recommend that:
- a. Women diagnosed with PAS can be cared for by obstetricians with experience in complex CDs in a local hospital close to the patient home.
 - b. Antenatal corticosteroids should be given for lung maturation at 30 weeks for planned delivery at 36-37 weeks of gestation.
 - c. No attempt should be made to remove the placenta (extirpative approach or forcible manual removal of the placenta) if it shows no signs of separation as this may cause substantial hemorrhage.
 - d. Conservative management or expectant management with adjuvant therapy such as methotrexate (MTX) should be considered in all cases of PAS.

a =F; b= F; c= T; d= F

Explanation to the answers for Question 3:

- a. Patients diagnosed with PAS should be cared for by a MDT with expertise in complex pelvic surgery in a specialist centre with logistic support for immediate access to blood products, adult and neonatal intensive care, using a preoperative coordination with protocol-based interdisciplinary care including anesthesiology, hematology/blood bank, maternal-fetal medicine, neonatology, and expert pelvic surgeons to optimize intraoperative and post-operative outcomes.
- b. As the timing of delivery decisions needs to balance maternal risks and benefits with those of the fetus or neonate and most patients presents with a placenta previa accreta antenatal, corticosteroids should be used for lung maturation following the international gestational age-based recommendations for anticipated delivery before term. Here the guidelines differ regarding the timing of delivery with the ACOG/SMFM recommending 34⁺⁰-35⁺⁶ weeks of gestation for scheduled cesarean delivery in a stable patient whereas for the RCOG, recommends delivery at 35⁺⁰-36⁺⁶ weeks of gestation in the absence of risk factors for preterm delivery
- c. Attempt at removing the placenta at delivery in case of PAS is inevitably associated with massive obstetric hemorrhage and a high maternal morbidity and some maternal mortality. If at the time of an elective repeat caesarean section, PAS is suspected based on uterine appearance and there are no extenuating circumstances mandating immediate delivery, the caesarean section should be delayed until until optimal surgical expertise arrives and adequate blood products are available rather than attempting at delivering the placenta.
- d. Conservative management or expectant management should be considered only for carefully selected cases of PAS after detailed counseling about the risks, uncertain benefits, and efficacy and local arrangements need to be made to ensure regular review, ultrasound examination and access to emergency care should the patient experience complications. MTX adjuvant therapy should not be used for expectant

management as it is of unproven benefit and has significant adverse effects, including maternal mortality.