

1 **Condensation:** *An evidence-based guideline from the International Society for abnormally*
2 *invasive placenta (AIP) for the antenatal and intra-partum management of AIP.*

3

4 **Short title:** *International Society for abnormally invasive placenta guideline for the*
5 *management of abnormally invasive placenta*

6

7

1 ABSTRACT

2 The worldwide incidence of abnormally invasive placenta is rapidly rising following the
3 trend of increasing caesarean delivery. It is a heterogeneous condition and has a high
4 maternal morbidity and mortality rate, presenting specific intra-partum
5 challenges. Its rarity makes developing individual expertise difficult for the majority of
6 clinicians. The International Society for Abnormally Invasive Placenta aims to improve
7 clinicians understanding and skills in managing this difficult condition. By pooling
8 knowledge, experience and expertise gained within a variety of different healthcare
9 systems the society seeks to improve the outcomes for women with abnormally
10 invasive placenta globally.

11 The recommendations presented herewith were reached using a modified Delphi
12 technique and are based on the best available evidence. The evidence base for each
13 is presented using a formal grading system. The topics chosen address the most
14 pertinent questions regarding intra-partum management of abnormally invasive
15 placenta with respect to clinically relevant outcomes including: Definition of a
16 center of excellence; requirement for antenatal hospitalization; antenatal optimization
17 of hemoglobin; gestational age for delivery; antenatal corticosteroid
18 administration; use of pre-operative cystoscopy, ureteric stents and prophylactic
19 pelvic arterial balloon catheters; maternal position for surgery; type of skin
20 incision; position of the uterine incision; use of inter-operative ultrasound; prophylactic
21 administration of oxytocin; optimal method for intra-operative diagnosis; use of
22 expectant management; adjuvant therapies for expectant management; use of local
23 surgical resection; type of hysterectomy; use of delayed hysterectomy; intra-operative
24 measures to treat life-threatening hemorrhage; fertility after conservative
25 management.

26

27

28 **Keywords:** *abnormally invasive placenta, accreta, guideline, increta, morbidly*
29 *adherent placenta, percreta, placenta, placenta accreta spectrum*

30

31

1 INTRODUCTION

2 Abnormally invasive placenta (AIP), also called placenta accreta spectrum disorder
3 (PAS), describes the clinical situation where a placenta does not separate
4 spontaneously at delivery and cannot be removed without causing abnormal and
5 potentially life-threatening bleeding^{1, 2}. There is increasing epidemiological evidence
6 demonstrating that the incidence of AIP is rising worldwide³. This is most likely due to
7 the rising rates of cesarean delivery, which is the greatest single risk factor for AIP in
8 subsequent pregnancies. Optimal management requires both accurate antenatal
9 diagnosis and a robust perinatal management strategy. However, even with the rising
10 incidence, AIP is still rare (0.79-3.11 per 1000 births after prior cesarean)⁴ and so
11 defining an optimal management strategy remains extremely challenging. The
12 literature contains a vast number of case reports, case-series and retrospective cohort
13 studies looking at multiple management strategies but most studies are small and
14 many are methodologically flawed limiting their utility. The situation is made even more
15 difficult by the spectrum of presentations being presented in most studies as a binary
16 outcome ('AIP' or 'not AIP') with varying diagnostic criteria and no attempted
17 assessment of severity².

18 The International Society for Abnormally Invasive Placenta (www.IS-AIP.org) evolved
19 from the European Working group on AIP (EW-AIP) and currently consists of 42
20 clinicians and basic science researchers from 13 countries. At the 11th meeting of
21 EW-AIP in Naples (2017) the IS-AIP (International Society for AIP) constitution was
22 formally agreed and the board elected. It was registered in Belgium on 12th October
23 2107 as a non-profit making association. The society has strict membership criteria
24 and a full constitution (see www.is-aip.org).

25 The aim of the IS-AIP is to promote excellence in all aspects of healthcare relating to
26 AIP including research (clinical, epidemiological and 'wet lab' based), clinical
27 diagnosis and management, education (including raising awareness with the general
28 population and healthcare providers especially with a view to prevention). The group
29 as the EW-AIP has already published standardized descriptors to aid in the
30 ultrasound diagnosis of AIP⁵. This paper aims to generate an evidence-based
31 recommendation for the intra-partum management of AIP using the unique,
32 international composition of the IS-AIP to provide expert consensus recommendation
33 where the evidence identified is weak, flawed or absent.

1

2 **METHODS**

3 The questions to be answered in this guideline were selected by a modified Delphi
4 technique. The IS-AIP membership were all invited to suggest issues which they felt
5 were pertinent to the management of AIP. These questions were then discussed in
6 detail at an IS-AIP meeting in Prague (October 2016) with the final decision on
7 inclusion being taken by a vote. All 21 questions addressed in this paper were
8 unanimous agreed to be important by the IS-AIP membership.

9 The search and assessment of the published evidence was then undertaken by an
10 individual IS-AIP member according to a predefined pro forma (Supplementary
11 material 1). In brief, this involved undertaking a full 'systematic review' process for
12 each topic including formulating an appropriate question specific to AIP using the
13 PICO framework⁶ and searching all relevant medical databases (PubMed, EMBASE,
14 CINAHL, Cochrane database etc.) and, where appropriate, some non-medical
15 databases (e.g. Google). All searches for the 21 different topics were undertaken at
16 various points during 2017. Full text versions of all potential papers were then
17 obtained, assessed for relevance and critically appraised using the levels of evidence
18 provided by the Centre for Evidence Based Medicine⁷.

19 All the completed pro formas detailing the formulated question, search strategy,
20 results and critical analysis for each topic were then sent to the entire membership for
21 consideration of the search strategy used and the resulting literature retrieved. Where
22 potential methodological issues were identified by another member (e.g. problems
23 with search terms usually relating to language differences (e.g. only searching
24 "ureteral" not "ureteric OR ureteral")), a second IS-AIP member repeated the search
25 to ensure no evidence had been missed. A few topics which revealed little high-
26 quality evidence during the original 2017 search were searched again in 2018 to
27 ensure that no further evidence had been published.

28 Once all the evidence had been identified the recommendations were reached by a
29 modified Delphi technique involving the entire membership of the IS-AIP. Each topic
30 was discussed face to face by the membership either at an IS-AIP meeting or using
31 web conferencing. A frank and open discussion concerning the available evidence
32 ensured that, to the best of our ability, any personal bias regarding the evidence was

1 removed and a fair interpretation of the data was recorded. Where possible, a
2 recommendation was then drawn up from the evidence, taking into account the
3 quality (level) of each piece of evidence. Where high quality evidence was scarce
4 and level 5 'expert opinion' required, each topic was then discussed until a tentative
5 consensus recommendation was reached. Each recommendation was then voted on
6 and only ratified if it received support from the group. On completion of the process,
7 all the recommendations were then circulated to the entire membership once again to
8 ensure unanimous ratification of all recommendations remained.

9 **RESULTS**

10 **1. What constitutes 'expertise' in management of AIP and/or defines a** 11 **'Center of Excellence'?**

12 Evidence for what constitutes an 'expert' in the management of AIP is missing from
13 the literature despite opening the search strategy to non-medical databases such as
14 Google. Therefore, the IS-AIP recommendation is based on a consensus opinion
15 (level 5 evidence) and is:

16 *An expert is a person with significant experience in AIP and a high level of knowledge*
17 *and/or skills relating to the condition (Grade D recommendation).*

18 Whilst there are multiple retrospective cohort studies demonstrating decreased
19 maternal morbidity when women are cared for in self-defined 'Centers of
20 Excellence'⁸⁻¹¹ there was no definitive evidence for what should constitute such a
21 'Center of Excellence'. Therefore, the IS-AIP recommendation is based on a
22 consensus opinion (level 5 evidence;) and is summarized in Table 1.

23 This recommendation was reached independently of the recently published FIGO
24 consensus statement¹² and USA consensus panel recommendation¹³ but is in
25 agreement with both.

26

27 **2. Is there evidence of reduced morbidity if women antenatally diagnosed** 28 **with AIP remain in hospital until delivery?**

29 Given the rarity of the condition many physicians feel uncomfortable managing
30 woman diagnosed with AIP as outpatients and therefore many are admitted to
31 hospital often for several weeks if not months. There were no studies identified which
32 specifically addressed the question of inpatient versus outpatient care for women

1 antenatally diagnosed with AIP. As the majority of AIP cases are also placenta
2 previa, an examination of the evidence available for placenta previa was also made.
3 There were five publications reporting outcomes for expectant outpatient
4 management of women with placenta previa (one small RCT¹⁴ and four retrospective
5 cohort studies¹⁵⁻¹⁸).

6 The oldest publication from 1984¹⁷ presented data from a retrospective cohort of 38
7 women. The authors suggested significant improvement in neonatal morbidity and
8 mortality for women with placenta previa who were managed as inpatients. However,
9 there appeared to be significant recruitment bias, with the woman managed as
10 outpatients being enrolled at significantly earlier gestations compared to those
11 managed as inpatients (poor quality cohort, level 4 evidence).

12 A subsequent small RCT by Wing et al¹⁴ reported the outcomes for 26 asymptomatic
13 women with placenta previa managed at home compared with 27 who were
14 hospitalized (low quality RCT, level 2b evidence). The only significantly different
15 outcome was length of hospital stay. Three retrospective cohort studies^{15, 16, 18}
16 examined the outcomes for a total of 305 women (acceptable and poor quality
17 cohorts, level 2b/4 evidence) and did not demonstrate any significant difference in
18 either maternal or neonatal outcomes. All three studies concluded that in selected
19 women with asymptomatic placenta previa outpatient management was both safe
20 and cost effective. However, these were all retrospective cohort studies and there
21 may have been individual circumstances which biased the selection of care settings
22 for the women involved. This evidence for outpatient management of placenta previa
23 was taken into consideration when reaching the consensus recommendation for the
24 management of AIP.

25 In conclusion, there is no evidence for antenatal hospitalisation of asymptomatic
26 women with antenatally diagnosed AIP, whether it is associated with placenta previa
27 or not. Therefore, the IS-AIP recommendation is extrapolated from the best available
28 evidence for inpatient management of placenta previa¹⁴ (level 2b evidence) and is as
29 follows:

30 *Expectant outpatient management of women with AIP, even in the presence of*
31 *placenta previa, is acceptable treatment, as long as the woman is asymptomatic and*
32 *has been appropriately counselled (Grade C recommendation). However, adequate*

1 *resources must be available to allow rapid return to the hospital (Grade D*
2 *recommendation).*
3 *Symptomatic women (for example those with bleeding, uterine contractions or other*
4 *obstetric complications) should be cared for according to local protocols and*
5 *expertise (Grade D recommendation).*
6

7 **3. Is there evidence of reduced morbidity in women antenatally diagnosed**
8 **with AIP if they receive iron supplementation to optimize hemoglobin**
9 **levels?**

10 In conditions with increased risk of severe bleeding at delivery most physicians will
11 take steps antenatally to ensure the woman's starting haemoglobin (Hb) level is as
12 high as possible in an attempt to reduce morbidity. There was no evidence available
13 for the benefit of antenatal optimization of Hb specifically for cases of AIP. A single
14 study was identified which looked to identify determinants of blood loss at childbirth.
15 This was a 'nested cohort study' whose participants had already been recruited to a
16 community based RCT of treatments for severe anaemia in women from Zanzibar.
17 This reported that women with Hb of <90g/L at delivery were at increased risk of
18 blood loss both at the time of birth and in the immediate postpartum period,
19 irrespective of mode of delivery¹⁹ (level 1b evidence). This study was taken into
20 consideration but it does not answer the original question posed therefore, the IS-AIP
21 recommendation is based on a consensus opinion (level 5 evidence) and is as
22 follows:

23 *As soon as women are antenatally diagnosed with AIP they should have their Hb*
24 *level measured. If it is low (<110g/l (11g/dl) before 28 weeks' gestation or <105g/l*
25 *(10.5 g/dl) after 28 weeks'), appropriate haematinic investigations should be*
26 *undertaken and if indicated, iron supplementation (oral or intravenous) should be*
27 *given to optimize their Hb level before surgery (Grade D recommendation).*

28 This recommendation was reached independently but is in agreement with the UK
29 RCOG prevention and management of postpartum hemorrhage guideline (Green-top
30 number 52)²⁰ and the recent FIGO consensus statement¹².

31

32 **4. At what gestation should women with antenatally diagnosed AIP be**
33 **delivered?**

1 Arranging an elective cesarean earlier than usual may reduce the risk of an
2 emergency delivery, however the increased risks to the neonate from prematurity
3 must also be considered. Six studies were found which reported maternal and
4 neonatal outcomes for different gestational ages at delivery in women with an
5 antenatal diagnosis of AIP^{9, 21-25}. All six were retrospective observational studies
6 (level 4 evidence). None of the studies provided any robust evidence for the optimal
7 gestational age for delivery for woman with AIP, to reduce maternal and neonatal
8 morbidity whilst still minimizing the rate of unplanned, emergency delivery.
9 Robinson and Grobman²⁶ published a decision analysis in 2010 recommending that
10 the optimal timing of delivery for women with placenta previa and ultrasound
11 suspicion of AIP was 34 weeks. Their aim was to define the gestation which balanced
12 the risks of prematurity with the risk of emergency delivery. The flaw with their
13 elegant model is that the risk of bleeding used to formulate the nine models was
14 based on 400 women with placenta previa only and not previa with AIP.
15 Therefore, although all these studies were taken into consideration, the IS-AIP
16 recommendation is based on a consensus opinion (level 5 evidence) and is as
17 follows:

18 *The timing of delivery should be tailored to each unique set of circumstances and*
19 *based on the individual woman's risk of emergent delivery. To reduce the risk of*
20 *neonatal morbidity it is reasonable to continue expectant management until after*
21 *36+0 weeks' gestation for women with no previous history of pre-term delivery*
22 *(<36+0 weeks) and who are stable with no vaginal bleeding, PPRM, or uterine*
23 *contractions suggestive of pre-term labor (Grade D recommendation).*
24 *In the case of women with history of previous pre-term birth, multiple episodes of*
25 *small amounts of vaginal bleeding, a single episode of a significant amount of vaginal*
26 *bleeding or PPRM, planned delivery at around 34+0 week's gestation should be*
27 *considered given the increased risk of emergent delivery (Grade D recommendation).*

28

29 **5. Is there evidence of reduced mortality or morbidity in neonates if women**
30 **with antenatally diagnosed AIP receive corticosteroids for delivery**
31 **occurring after 34+0 weeks' gestation?**

32 The issue of administration of corticosteroids for preterm delivery after 34+0 gestation
33 is contentious. It is unclear whether AIP itself makes the neonate more likely to

1 experience respiratory distress. No prospective RCT exists evaluating the influence
2 of AIP *per se* on neonatal respiratory morbidity beside the normal influence of
3 prematurity when delivered between 34⁺⁰ and 37⁺⁰ weeks of gestation. One
4 retrospective case series (level 4 evidence) of histopathologically diagnosed AIP
5 compared the neonatal outcomes between antenatally diagnosed AIP and AIP cases
6 diagnosed intrapartum²⁵. Although there was no significant difference between the
7 gestation at delivery (33.9 vs 34.7 weeks; p=0.34) for the two groups, those
8 antenatally diagnosed were more likely to have received antenatal steroids (65% vs
9 16%; p<0.001) yet still demonstrated a higher rate of admission to the neonatal
10 intensive care unit (86% vs 60%; p=0.005), and longer neonatal hospital stays (11 vs
11 7 days; p=0.006). Interpretation of this dataset is difficult with regard to the specific
12 question as there are likely to be considerable confounding factors.

13 There was no evidence available that the presence of AIP itself increases neonatal
14 respiratory morbidity or mortality if the scheduled delivery takes place between 34⁺⁰
15 and 37⁺⁰ weeks of gestation. Therefore, the IS-AIP recommendation for antenatal
16 glucocorticoid treatment to induce fetal lung maturation for a scheduled delivery after
17 34⁺⁰ weeks of gestation is based on consensus opinion (level 5 evidence) and is as
18 follows:

19 *An individualized approach for antenatal steroid administration should be employed,*
20 *based on the current local guidelines for the specific gestation at delivery,*
21 *irrespective of the suspicion or diagnosis of AIP (Grade D recommendation).*

22 **6. Does routine pre-operative cystoscopy improve the accuracy of**
23 **antenatal diagnosis of AIP and/or reduce maternal morbidity in women**
24 **with antenatally diagnosed AIP?**

25 Pre-operative cystoscopy to assess for bladder wall involvement is recommended by
26 many operators, others argue that it adds no useful information whilst increasing the
27 time in the operating room and the risks of infection and lower urinary tract trauma.
28 No RCTs were found examining the efficacy of pre-operative cystoscopy for the intra-
29 partum management of AIP. One case series presented 12 patients with AIP and
30 gross hematuria (level 4 evidence) who underwent pre-operative cystoscopy²⁷. The
31 authors reported that the procedure did not help to establish a preoperative diagnosis
32 in any patient and concluded that cystoscopy had minimal diagnostic value.

1 The evidence that cystoscopic findings, even in the presence of gross hematuria, do
2 not correlate to the level of bladder involvement was taken into account but, given the
3 poor quality of the study, the recommendation is supported by consensus opinion
4 (level 5 evidence).

5 *The IS-AIP does not recommend undertaking routine pre-operative cystoscopy. If*
6 *pre-operative cystoscopy is performed for insertion of ureteric stents, the appearance*
7 *of the bladder should not change the (imaging-based) plan of management (Grade D*
8 *recommendation).*

9

10 **7. Does routine ureteric stent placement reduce maternal morbidity in** 11 **cases of antenatally diagnosed AIP?**

12 Ureteric stents may aid identification of the ureter and prevent inadvertent transection
13 or ligation at hysterectomy, but insertion has its own risks such as urinary tract
14 perforation and infection. One retrospective cohort study²⁸ (level 2b evidence), of 57
15 cases of suspected AIP and 19 undiagnosed cases reported on ureteric stenting and
16 unintentional urinary tract injury. Ureteric stenting was attempted in 25 of the
17 suspected cases. The stent placement was achieved bilaterally in only 17/25 (68%)
18 of cases, on only one side in 4/25 (16%) of cases, and neither side in 4/25 (16%).

19 Women with bilateral ureteral stents had a lower incidence of early morbidity
20 compared with women without stents (3/17 (18%) vs. 22/40 (55%), $p = 0.018$). A non-
21 significant reduction in ureteric injury was observed (0 vs. 7%).

22 A systematic review of 49 case series and case reports (level 3a evidence), including
23 the above cohort study, attempted to examine the efficacy of approaches aimed at
24 minimizing urinary tract injuries in AIP²⁹. Of the 292 women with AIP, whether ureteric
25 stents were successfully placed or not, was reported for 90 cases only. No details
26 were available on the number in whom it was attempted but unsuccessful. The risk of
27 urinary tract injury was significantly lower in the group with ureteric stents in situ, 2/35
28 (6%) compared to those who were known not to have stents, 18/55 (33%;
29 $p=0.01$).

30 Neither study provided robust evidence regarding the severity of AIP which most
31 benefited from stent placement therefore the recommendation is also supported by
32 consensus opinion (level 5 evidence) and is:

1 *Placement of ureteric stents may be beneficial in preventing ureteric injury and early*
2 *morbidity (Grade B recommendation). However, given the potential risks associated*
3 *with stent placement, the evidence is not strong enough to recommend routine*
4 *placement of ureteric stents for all suspected cases of AIP. The benefit from ureteric*
5 *stents is probably limited to cases of percreta with significant invasion where*
6 *hysterectomy is likely to be highly complex (Grade D recommendation).*
7

8 **8. Does routine insertion of prophylactic balloon catheters into the pelvic**
9 **vasculature reduce maternal morbidity in cases of antenatally diagnosed**
10 **AIP?**

11 A main management objective for AIP is reduction of blood loss. Endovascular
12 balloon occlusion of the pelvic circulation has been proposed as a method of
13 achieving this. Given the aberrant blood supply often seen in AIP as a result of the
14 extensive neovascularization, however, occluding some of the pelvic vessels might
15 exacerbate bleeding from the collateral circulation. Therefore, the benefits of arterial
16 occlusion may not outweigh the associated risks of vessel rupture and
17 thromboembolism.

18 A systematic review has recently been published looking at endovascular
19 interventional modalities for hemorrhage control in AIP³⁰. This included both
20 prophylactic arterial balloon occlusion of different vessels, including the abdominal
21 aorta, and pelvic vasculature embolization either alone or together. Only 16 of the 69
22 included studies were controlled with the remaining being low quality cohort, case
23 series or case studies. The heterogeneity of the studies was reported by the authors
24 to be significant (review level 2a/3a evidence). All grades of AIP
25 (accreta/increta/percreta) were grouped together for the meta-analysis with no
26 differentiation in severity, with some studies including only balloon occlusion and
27 others using vascular embolization as well. The authors concluded that
28 “endovascular intervention is effective in controlling hemorrhage in abnormal
29 placentation deliveries”.

30 One small RCT (level 1b evidence)³¹ was found that had been included in the
31 systematic review³⁰. This randomized 27 women with AIP and showed no difference
32 in the number of packed red blood cell (RBC) units transfused for women who

1 underwent placement of balloon catheters in the iliac arteries compared to those who
2 did not or any other reduction in morbidity. This RCT however, also reported that
3 15% of the women with balloon catheters experienced an interventional radiology
4 (IR) related complication.

5 The IS-AIP considered the findings of both these two studies. The RCT is a much
6 smaller data set but is more methodologically rigorous (level 1b evidence). The
7 systematic review, whilst larger is very heterogeneous, includes data of very low
8 quality and may be open to significant bias (level 2a/3a evidence). Therefore, taking
9 into account these two studies the IS-AIP recommendation is as follows:

10 *The effect of prophylactic arterial balloon catheters on bleeding and morbidity among*
11 *women with a prenatal diagnosis of AIP has yet to be confirmed. Significant adverse*
12 *events have been reported from this procedure. Larger, prospective, appropriately*
13 *controlled studies are needed to demonstrate both the safety and efficacy of*
14 *prophylactic balloon occlusion. Given this, the IS-AIP cannot recommend routine use*
15 *of prophylactic pelvic arterial balloon catheters for all cases of suspected AIP (Grade*
16 *B recommendation).*

17 This recommendation was reached independently of the recently published FIGO
18 consensus statement¹² but is in agreement with it.

19 **9. Is there an optimal maternal position for surgical delivery of women with** 20 **antenatally diagnosed AIP?**

21 Some operators suggest that women should be placed in the lithotomy position to aid
22 assessment of vaginal blood loss and facilitate manipulation of the cervix during
23 hysterectomy. However, prolonged periods of time in stirrups may lead to
24 compartment syndrome and obstetric neuropraxia. There are no publications which
25 specifically address the question of maternal position for surgery for women with AIP.
26 Therefore, the IS-AIP recommendation is based on consensus opinion (level 5
27 evidence) and is as follows:

28 *When hysterectomy is either planned or likely, the woman should be placed in a*
29 *position where the vagina is accessible (such as lithotomy or legs straight on the*
30 *operating table but parted) to facilitate manipulation of the cervix, if required to assist*
31 *the hysterectomy. This will also allow easier assessment of any blood lost vaginally*
32 *(Grade D recommendation).*

1 **10. Does routine vertical midline incision instead of using a transverse**
2 **incision reduce maternal morbidity in cases of antenatally diagnosed**
3 **AIP?**

4 Many operators advise routine use of a vertical skin incision to facilitate access to the
5 fundus and pelvic walls. However, a transverse incision may heal faster and reduce
6 the risk of incisional hernia, as well as being more cosmetically pleasing for the
7 woman. No studies were found comparing either maternal or fetal outcomes for
8 different skin incisions. In the few publications that mention the type of skin incision,
9 vertical midline incision appears to be used most frequently and is often anecdotally
10 recommended. Other transverse incisions, such as Pfannenstiel and Maylard, have
11 been reported and are recommended based on both aesthetic considerations and the
12 potential for a reduction in post-surgical complications. Given the lack of evidence,
13 the IS-AIP recommendation is based on consensus opinion (level 5 evidence) and is
14 as follows:

15 *There is no evidence of benefit for routine use of a vertical, midline incision for all*
16 *cases of antenatally diagnosed AIP. The decision regarding which type of skin*
17 *incision is used, should be made by the operating team. The location of the placenta,*
18 *degree of invasion suspected, likelihood of intraoperative complications, maternal*
19 *body habitus, gestational age and preference of the operating surgeon/obstetrician,*
20 *should all be taken into consideration (Grade D recommendation).*

22 **11. Does making a uterine incision in the upper segment to avoid**
23 **transecting the placenta reduce maternal morbidity in cases of**
24 **antenatally diagnosed AIP?**

25 One of the main surgical strategies in AIP is making the uterine incision away from
26 the placental bed, often in the fundus. However, gaining access to the fundus may
27 require a larger skin incision. One retrospective case series (level 4 evidence)³²
28 reported blood loss after transverse fundal uterine incision to avoid the placenta in 34
29 women with placenta previa, 19 of whom had intraoperatively confirmed AIP. The
30 average blood loss reported was 1,370g. There was no control group and the
31 severity of AIP was not reported, yet the authors conclude that this blood loss
32 “compares favourably with the volume lost during a routine transverse lower segment

1 section performed in patients without placenta previa or accreta". It is not possible to
2 draw any firm conclusion from this study therefore the IS-AIP recommendation is
3 based on expert consensus (level 5 evidence) and is as follows:

4 *Avoiding placental transection when making the uterine incision is essential if AIP is*
5 *clearly evident on opening the abdomen, and is reasonable for women with*
6 *antenatally suspected AIP but with no definite evidence seen at laparotomy, even if it*
7 *means making an upper segment or fundal incision, as it is likely to reduce maternal*
8 *blood loss from the placental bed (Grade D recommendation).*

9 **12. Does routine intraoperative ultrasound (US) to map the placental edges**
10 **before uterine incision reduce maternal morbidity in cases of antenatally**
11 **diagnosed AIP?**

12 Several reports in the literature anecdotally recommend the use of intraoperative US,
13 usually with the probe directly placed on the uterus protected by a sterile cover to
14 enable the upper edge of the placenta to be identified. This is often mapped out with
15 small, superficial diathermy marks. There is however, a theoretical risk of introducing
16 infection. No publications were found which address either the risks or benefits of
17 intraoperative ultrasound scanning for placental localization in women with suspected
18 AIP. One study by Al-Khan et al.⁹ retrospectively analyzed patients before and after
19 an institutional protocol for AIP management was introduced. In their protocol,
20 intraoperative US for placental localization is performed but the improvement in
21 outcomes cannot be directly attributed to any individual measure. Therefore, the IS-
22 AIP recommendation is based on a consensus of experts (level 5 evidence) and is as
23 follows:

24 *If the US scan is undertaken in an appropriately sterile manner, the small theoretical*
25 *risk of introducing infection is outweighed by the benefit of ensuring the incision is*
26 *made away from the placental bed. Therefore, intraoperative US of the exposed*
27 *uterus should be used, where possible, to locate the placental edge and assist*
28 *decision-making regarding the uterine incision site (Grade D recommendation).*
29

30 **13. Does routine prophylactic administration of oxytocin after delivery of the**
31 **baby reduce maternal morbidity in cases of antenatally diagnosed AIP?**

1 There is evidence for the prophylactic administration of oxytocin after delivery at
2 routine cesarean delivery to prevent PPH³³. However, the use of routine oxytocin at
3 cesarean in cases of antenatally suspected AIP, has not been addressed in any
4 study. Therefore, the IS-AIP recommendation is based on a consensus of experts
5 (level 5 evidence) and is as follows:

6 *Prophylactic administration of oxytocin immediately after delivery increases*
7 *contraction of the uterus which could be helpful for the assessment of placental*
8 *separation. If the whole placental bed is abnormally invasive, uterine contraction will*
9 *not result in any placental separation. If, however, the placenta is only partially*
10 *adherent or invasive, uterine contraction may cause some separation leading to*
11 *increased blood loss which could prompt the surgeon to either forcibly remove the*
12 *rest of the placenta or perform a more hurried hysterectomy. In light of this risk, the*
13 *IS-AIP recommend that when AIP is suspected antenatally, prophylactic uterotonic*
14 *agents should not be routinely given immediately after delivery of the infant. Instead a*
15 *full assessment should be made in accordance with the intraoperative diagnosis*
16 *recommendations (see next topic). Only if the placenta is removed, either fully or*
17 *partially, or there is already significant bleeding, should uterotonics be given (Grade*
18 *D recommendation).*

19

20 **14. Is there an optimal method for intrapartum clinical diagnosis of AIP?**

21 Whilst AIP can be suspected antenatally, ultimate confirmation only occurs when the
22 placenta fails to separate after delivery of the baby. Attempts to forcibly remove an
23 AIP may lead to catastrophic hemorrhage, hence reliable diagnostic signs are highly
24 desirable. No evidence was found for which clinical diagnostic method best correlates
25 with the gold-standard histopathological diagnosis therefore, the IS-AIP
26 recommendation is based on a consensus of experts (level 5 evidence) and is as
27 follows:

28 *The IS-AIP agree with the ACOG recommendation (level 5 evidence) that given the*
29 *high risk of false positives with all methods of antenatal diagnosis there must be*
30 *robust intra-partum evidence that there is actually significant AIP before surgical*
31 *treatment is commenced. Care must be taken however, that major hemorrhage is not*

1 *caused by inappropriate attempts to manually remove an AIP. The IS-AIP*
2 *recommend the following methods for clinically diagnosing AIP:*

3

4 ***Diagnosis of AIP after vaginal delivery:***

5 *The diagnosis of AIP should not be made if the placenta spontaneously separates*
6 *and is delivered by maternal effort, controlled cord traction or simple manual removal*
7 *of an already separated placenta, even if there is a subsequent diagnosis of retained*
8 *products of conception (RPOC). For the diagnosis of AIP, a manual removal of*
9 *placenta is required and at the time of manual exploration of the uterine cavity, in the*
10 *opinion of a senior, experienced obstetrician, no plane of cleavage can be identified*
11 *between the placenta and the myometrium. This can be for the entire placenta bed or*
12 *just in 'focal' areas. Major hemorrhage after piecemeal removal, removal of a 'ragged*
13 *placenta' or discovery of subsequent RPOC is not sufficient to make the diagnosis of*
14 *AIP (Grade D recommendation).*

15

16 ***For diagnosis of AIP after laparotomy at stepwise process should be followed:***

17 *Step 1: On opening the abdomen the external surface of the uterus and the pelvis*
18 *should be thoroughly inspected for frank signs of AIP which include:*

- 19
 - *Uterus over the placental bed appears abnormal (can have a bluish/purple*
20 *appearance) with obvious distension (a 'placental bulge'). See Figure 1.*
 - *Placental tissue seen to have invaded through the surface of the uterus. This*
21 *may or may not have penetrated the serosa. See Figure 2.*

22 *NB Care should be taken not to confuse this with a 'uterine window' which is*
23 *a uterine scar dehiscence with the placenta visible directly underneath it. If it*
24 *is a 'uterine window' the surrounding uterine tissue will appear normal. See*
25 *Figure 3.*

- 26
 - *Excessive, abnormal neo-vascularity in the lower segment (particularly with*
27 *vessels running cranio-caudally in the peritoneum). See Figure 4.*

28 *If these are clearly seen, AIP can be diagnosed confidently without recourse to any*
29 *further procedures (Grade D recommendation).*

30 *Step 2: If these are not seen, then the uterine incision should be made according to*
31 *the level of suspicion for AIP (see separate topic above). If the incision has been*
32 *placed such that the placenta is undisturbed, then gentle cord traction should be*
33

1 *attempted. If traction on the umbilical cord causes the uterine wall to be visibly pulled*
2 *inwards in the direction of traction without any separation of the placenta (the 'dimple'*
3 *sign) and there is apparent contraction of the uterus separate from the placental bed,*
4 *then AIP can be diagnosed (Grade D recommendation).*

5 *Step 3: If AIP has not been diagnosed by the previous 2 steps, then gentle digital*
6 *exploration can be attempted to assess if there is a plane of cleavage (following*
7 *method for diagnosis of AIP described for vaginal delivery). Care must be taken to*
8 *avoid causing hemorrhage (Grade D recommendation).*

9
10 In an attempt to assess severity, the IS-AIP use the clinical grading score in Table 2.
11 A version of this grading scale is also recommended by the recently published FIGO
12 guidelines³⁴.

13 **15. Is expectant management of clinically confirmed AIP effective and does**
14 **it reduce maternal morbidity when compared to surgical treatment**
15 **options?**

16 The 'leaving the placenta in situ' approach, or expectant management, consists of
17 leaving the entire placenta untouched and waiting for its complete resorption.
18 Attempting forcible removal of the placenta significantly increases blood loss,
19 hysterectomy rates, infection and disseminated intravascular coagulation³⁵ (level 2b
20 evidence).

21 Kutuk et al³⁶ recently published a retrospective cohort study comparing women
22 undergoing hysterectomy without placental removal (n=20), expectant management
23 (n=15), and placental removal with uterus conserving surgery (n=11) (level 2b
24 evidence). Two cases of percreta were planned to be uterus conserving surgery but
25 management was changed to expectant when the surgeons found that the placenta
26 had infiltrated the parametrium and the cervix. There was significantly lower blood
27 loss in the expectantly managed group (400 (250-2500) mL) than in both
28 hysterectomy (2000 (500-3500) mL; p<0.001), and uterus conserving surgery groups
29 (3000 (1100-4000) mL; p<0.001). None of the expectantly managed women received
30 blood products compared with transfusions of 700 (200–2400) mL packed RBC in the
31 hysterectomy group and 1200 (400–1800) mL in the uterus conserving surgery
32 group. Uterine preservation rates were not significantly different between the

1 expectantly managed women and those having uterus conserving surgery (14/15
2 [93%] vs 33/37 [89%]; $P>0.99$).

3 Most studies use avoidance of hysterectomy as the outcome measure of successful
4 expectant management. The single largest case series of expectant management
5 published to date is a multicenter retrospective study which included 167 cases of
6 AIP in 40 teaching hospitals (level 2b evidence)³⁷. The overall success rate of uterine
7 preservation was 78% (95% CI 71–84%), with severe maternal morbidity reported in
8 10 cases (6%). An empty uterus was obtained spontaneously in 75% of cases with
9 additional hysteroscopic resection and/or curettage performed in 25%. One maternal
10 death occurred as a direct result of methotrexate injection into the umbilical cord. As
11 no hysterectomy specimens were available for histopathological confirmation, a
12 criticism of this study is that some women may not actually have had an AIP.
13 However, an experienced acoucher should be able to diagnose the vast majority of
14 AIP cases clinically at laparotomy (See point 14) and subsequent histopathological
15 findings from cases of 'failed' expectant management suggest that the risk of
16 misdiagnosis is very low. For this case series,³⁷ histopathological examination
17 confirmed the diagnosis of AIP in all the immediate hysterectomies (18/18) and all but
18 1 in the delayed hysterectomies (17/18).

19 Another smaller study of 36 women managed conservatively reported a success rate
20 of 69%³⁸ (level 2b evidence). Three reviews of published case series report success
21 rates of 85%³⁹, 58%⁴⁰ and 60%⁴¹. Care must be taken interpreting this as these are
22 not independent reviews, many cases are included in all three studies (level 4
23 evidence).

24 The IS-AIP recommendation is as follows:

25 *When expectant management is planned and AIP confirmed at delivery, forced*
26 *manual removal of the placenta should not be attempted (Grade B recommendation).*
27 *Expectant management appears to be associated with less blood loss and lower*
28 *transfusion requirements than both hysterectomy and uterus conserving surgery and*
29 *will be successful for between 60% to 93% of women with the remainder undergoing*
30 *hysterectomy, usually for secondary PPH or infection (Grade B recommendation).*
31 *Therefore, this is an appropriate management strategy for women wishing to*
32 *preserve their fertility and in cases where hysterectomy is considered to be at very*
33 *high risk of surgical complications. If women choose this option they must be*

1 *appropriately counselled including being informed that there is a 6% risk of severe*
2 *maternal morbidity (Grade B recommendation).*

3 **16. If expectant management is undertaken for women with AIP does the use**
4 **of adjuvant therapies such as methotrexate and pelvic arterial**
5 **embolization increase efficacy?**

6 ***Methotrexate***

7 Methotrexate has been suggested to accelerate placental resorption in cases of
8 conservative management. There is no reliable evidence to support the use of
9 methotrexate in cases of AIP left *in situ*. Only case reports and small case series with
10 no control groups have been reported (level 4 evidence) therefore it is impossible to
11 assess efficacy. Severe adverse effects such as pancytopenia and nephrotoxicity
12 have been described with methotrexate³⁷. One case of maternal death directly
13 related to methotrexate was reported among the 21 patients who received
14 methotrexate in the largest retrospective cohort of 167 women³⁷ (level 2b evidence).
15 The IS-AIP recommendation is therefore:

16 *There is no evidence of benefit from the use of methotrexate when the placenta left in*
17 *situ. As there is evidence for potential significant harm including maternal mortality,*
18 *the IS-AIP do not recommend the use of methotrexate for conservative management*
19 *of AIP (Grade B recommendation).*
20

21 ***Pelvic arterial embolization***

22 Prophylactic pelvic embolization has also been used to prevent severe PPH and
23 secondary hysterectomy in cases of conservative management. However, the risks of
24 morbidity from embolization may outweigh its potential benefit. A systematic review
25 published in 2015, included eleven individual studies (mostly poor cohorts or case
26 series) reporting on 177 cases of uterine artery embolization in women with AIP with
27 planned conservative management⁴² (level 3a evidence). Hysterectomy was avoided
28 in 159 of these women (90%). The review did not report maternal morbidity other
29 than to say “all patients survived”.

30 A retrospective cohort study of 45 patients with AIP compared prophylactic artery
31 uterine embolization to no embolization for women undergoing conservative
32 management⁴³ (level 2b evidence). No difference was observed in blood loss,

1 hysterectomy rates or incidence of massive transfusion. However, one patient in the
2 embolization group had uterine necrosis requiring hysterectomy.

3 A retrospective cohort of 12 patients having embolization to assist conservative
4 management reported uterine necrosis requiring hysterectomy in one women⁴⁴ (level
5 2b evidence). This study was included in the systematic review⁴².

6 The IS-AIP recommendation is therefore:

7 *There is no evidence for prophylactic uterine artery embolization increasing efficacy*
8 *of conservative management and two cases of uterine necrosis have been reported*
9 *in two cohort studies (level 2b evidence). Therefore, the IS-AIP do not recommend*
10 *prophylactic uterine artery embolization in women undergoing conservative*
11 *management (Grade B recommendation). However, therapeutic embolization for*
12 *postpartum hemorrhage in conservatively managed women may avoid hysterectomy*
13 *(Grade D recommendation).*

14

15 **17. Does local surgical resection (uterus conserving surgery) reduce**
16 **maternal morbidity in women antenatally diagnosed with AIP when**
17 **compared to other treatment options including hysterectomy and**
18 **conservative management?**

19 Surgical removal of part of the myometrium where the placenta is abnormally
20 attached (local surgical resection) has been proposed as a technique for managing
21 AIP whilst conserving the uterus. Eleven original publications were found that
22 reported on a variety of local resection techniques, seven were retrospective cohort
23 studies, three prospective studies and 1 review. Only one retrospective cohort study⁴⁵
24 (level 2b evidence), compared planned hysterectomy to local resection and found
25 less bleeding in the local resection group measured as packed RBC transfusion (1.1
26 units compared with 2.2 units; $P < 0.05$). One retrospective cohort study⁴⁶ (level 2b
27 evidence), compared a peripartum local resection technique known as the 'Triple-P'
28 procedure to conservative management leaving the placenta partly or entirely in the
29 uterus. Blood loss was lower in the 'Triple-P' group ($1700 \pm 950\text{mL}$ vs $2170 \pm 246\text{mL}$)
30 but this difference was not statistically significant ($P = 0.445$). The need for
31 emergency peripartum hysterectomy was significantly lower in women undergoing

1 the 'Triple-P' procedure than in the control group (0/19 (0.0%) vs 3/11 (27.3%), $P =$
2 0.045).

3 Wei et al⁴⁷ published a retrospective, cohort study of 96 patients with
4 histopathologically confirmed AIP who were treated by local resection with (n=45) or
5 without (n=51) a Foley catheter tied around the lower uterine segment to enhance
6 haemostasis (level 2b evidence). Use of the Foley catheter appeared to reduce blood
7 loss and possibly also the hysterectomy rate (0 vs. 3).

8 Clausen et al⁴⁸ published a retrospective consecutive case series of placenta
9 percreta treated with either hysterectomy or local resection (level 4 evidence). Of the
10 11 women requesting fertility preservation, nine were successfully treated with local
11 resection with a blood loss of 1,300 to 6,000 mL. The eight women undergoing
12 hysterectomy had a blood loss of 450 to 16,000 mL. The difference in blood loss
13 between the two treatments, however, does not reflect intention to treat. The one
14 woman who had a 16,000mL blood loss had requested fertility preservation and local
15 resection was attempted initially followed by a hysterectomy as the placenta had
16 invaded into the cervix and parametrium.

17 Kutuk et al³⁶ published a retrospective cohort study comparing women undergoing
18 hysterectomy without placental removal (n=20), expectant management (n=15), and
19 women who underwent placental removal and uterine conserving surgery (n=11)
20 (level 2b evidence); see the topic on expectant management for further details.

21 In all of the other studies the intended surgical procedure was local resection and
22 there was no comparator group⁴⁹⁻⁵⁴. The success rates for avoiding hysterectomy
23 ranged between 67% and 100%.

24 In 2014 Clausen et al. published a review of 119 patients with placenta percreta
25 stratified by mode of management⁴⁰ (level 3a evidence): 17 cases reported were
26 local resection with no secondary hysterectomies; 36 cases were conservatively
27 managed, of these 3 underwent a planned delayed hysterectomy and 18 had
28 emergency hysterectomies; 66 had primary cesarean hysterectomies. Local
29 resection was reported to be associated with a lower rate of complications including
30 urinary tract injury, secondary hemorrhage and infection. However, there was no
31 information provided regarding how the choice for local resection was made.

32 The evidence available for the efficacy of local resection is complicated by selection
33 bias and poor comparator groups making interpretation of the results difficult.

1 However, the IS-AIP recommendation based on the available evidence and
2 supported by consensus opinion, is as follows:

3 *There is no evidence to demonstrate that routine local resection in all cases of AIP*
4 *reduces maternal morbidity or mortality compared to other treatment methods.*

5 *However, in appropriately selected cases, local resection appears to be reasonably*
6 *successful (level 2b evidence) and may reduce blood loss and maternal morbidity*
7 *compared to hysterectomy (level 2b/4 evidence) and requirement for emergency*
8 *hysterectomy compared with conservative management (level 3b evidence).*

9 *Therefore, local resection should be considered in appropriately selected cases*
10 *(Grade B recommendation).*

11 *There is however, some evidence to suggest that attempting local resection may be*
12 *detrimental in cases involving invasion into the uterine cervix and/or parametrium*
13 *(level 4 evidence). Therefore, local resection should only be considered where there*
14 *is no invasion into the parametrium and/or uterine cervix (Grade C recommendation).*

15 *The IS-AIP expert consensus of what constitutes an ‘appropriate case’ for local*
16 *resection is focal disease with an adherent/invasive area which is <50% of the*
17 *anterior surface of the uterus (Grade D recommendation). More evidence is required*
18 *to fully identify which women will most benefit from this management strategy.*

19

20 **18. Does performing a sub-total hysterectomy reduce maternal morbidity in**
21 **women antenatally diagnosed with AIP when compared to total**
22 **hysterectomy?**

23 Sub-total, or supracervical, hysterectomy has been reported to be associated with
24 lower maternal morbidity than total hysterectomy, particularly in pregnant women.
25 Whilst several studies on AIP reported the actual numbers of sub-total and total
26 hysterectomy performed in their cohorts, no evidence for the benefit of one type of
27 hysterectomy compared to another was presented. Wright et al⁵⁵ reported on a
28 retrospectively collected cohort of 4967 peripartum hysterectomies performed in the
29 USA (level 2b evidence). AIP was the stated indication for 1789 (36%) of these
30 hysterectomies. No sub-group analysis of the AIP cases was presented. For the
31 overall dataset of all peripartum hysterectomies, total hysterectomy was associated
32 with more bladder injuries (10.2% vs. 7.2%, P<0.001), an increased number of other

1 operative injuries (10.4% vs. 8.3%, $P=0.02$), more gastrointestinal complications
2 (7.9% vs. 6.3%, $P=0.04$) and a longer hospital stay ($P<0.001$). Sub-total
3 hysterectomy was associated with more secondary operations (5.0% vs. 3.6%,
4 $P=0.02$), higher rates of transfusions (52.4% vs. 42.7%, $P<0.001$) and a higher
5 perioperative maternal death rate (1.4% vs. 0.8%, $P=0.04$).

6 Knight et al, on behalf of the UK Obstetric surveillance system (UKOSS), examined
7 all the peripartum hysterectomies occurring in the UK over a 12 month period⁵⁶ (level
8 2b evidence). For the 318 hysterectomies performed there were no significant
9 differences in outcomes between total and subtotal hysterectomy. One hundred and
10 nineteen of the hysterectomies were performed for AIP, these were more commonly
11 total hysterectomies but no sub-group analysis between the two methods was
12 reported.

13 Another six small retrospective studies were identified (level 3b/4 evidence). Ogunniyi
14 et al reported 32 cases of peripartum hysterectomy⁵⁷ and demonstrated that sub-total
15 hysterectomy was associated with higher post-operative morbidity than total (55.6%
16 vs 71.4%; $p<0.01$). Roopnarinesingh et al. reported 52 cases in a single center in
17 Dublin⁵⁸. They found that total hysterectomy was associated with a significantly
18 higher transfusion rate (12.7 units vs. 9.4units; $P<0.001$). Saeed et al reported on 39
19 cases from a single center in Pakistan⁵⁹ and found that total hysterectomy had a
20 significantly higher number of postoperative complications than sub-total.

21 D'Arpe et al. reported on 51 cases from a single center in Italy⁶⁰, Daskalakis et al.
22 reported 45 cases from a single center in Athens⁶¹ and Olamijulo et al reported on 34
23 cases from a single center in Nigeria⁶². No significant differences in morbidity were
24 found in these studies (level 4 evidence).

25 No information was available in any study regarding how the decision was made
26 regarding the method of hysterectomy. Therefore, the evidence available is highly
27 likely to be complicated by considerable selection bias making interpretation of these
28 results extremely difficult. Therefore, the IS-AIP recommendation is also supported
29 by consensus opinion (level 5 evidence):

30 *There is no evidence to demonstrate that routine sub-total hysterectomy in all cases*
31 *of AIP reduces maternal morbidity or mortality compared to total hysterectomy, in fact*
32 *the largest study published suggested that sub-total might be associated with a*
33 *higher maternal mortality rate (level 2b evidence).*

1 *The type of hysterectomy performed therefore, should be individualized on a case by*
2 *case basis, taking into account the site and degree of invasion both suspected*
3 *antenatally and found at laparotomy, amount of bleeding, stability of the woman, and*
4 *the skills, experience and preference of the operating team (Grade C*
5 *recommendation). In cases with cervical invasion total hysterectomy should be*
6 *performed (Grade D recommendation).*

7

8 **19. Does performing a planned delayed hysterectomy reduce maternal**
9 **morbidity in women antenatally diagnosed with AIP when compared to**
10 **hysterectomy at the time of cesarean?**

11 A planned delayed hysterectomy involves leaving the placenta untouched in the
12 uterus at the time of delivery with the intention of performing a hysterectomy at a later
13 date (days to weeks) after the cesarean delivery. This is performed in an attempt to
14 reduce morbidity from the hysterectomy as the uterine perfusion reduces after
15 delivery of the baby even with the placenta in situ. Only one retrospective study was
16 identified that attempted to compare planned delayed hysterectomy with immediate
17 hysterectomy⁶³. However, all the immediate hysterectomy cases presented as
18 emergencies without antenatal diagnosis and with signs of shock from hemorrhage.
19 The delayed cases were all antenatally diagnosed and underwent delivery in a
20 haemodynamically stable condition (poor quality cohort, level 4 evidence).
21 This study was taken into consideration but as it is methodologically flawed, the IS-
22 AIP recommendation is based on a consensus opinion (level 5 evidence) and is as
23 follows:

24 *Given the evidence for the success of expectant management for AIP, the IS-AIP*
25 *recommend that the surgical choice should be between immediate surgical*
26 *management (hysterectomy or local resection) and expectant management. There is*
27 *no evidence of benefit of planned delayed hysterectomy, and the potential*
28 *complications of performing a second intentional surgical procedure in a stable*
29 *patient, outweigh the benefits (Grade D recommendation).*

30

1 **20. What are the most effective intra-operative measures to treat life-**
2 **threatening massive hemorrhage in women with AIP should it occur at**
3 **the time of delivery?**

4 Strategies for massive bleeding from AIP vary according to operator experience and
5 resources available. We found no RCTs providing direct comparison of different
6 intraoperative strategies to reduce blood loss in the event of life-threatening
7 hemorrhage.

8 *Pharmacological treatments*

9 There were no publications that specifically addressed the question of the
10 effectiveness of uterotonics or hemostatic/pro-coagulant agents as life-saving
11 measures to treat massive hemorrhage directly attributable to AIP. Therefore, the IS-
12 AIP recommendation is based on consensus opinion (level 5 evidence) and is as
13 follows:

14 *Uterotonics should be considered in accordance with local protocols whenever*
15 *massive uterine bleeding occurs until either hemostasis is achieved or the uterus is*
16 *removed. Hemostatic/pro-coagulant agents can also be used in accordance with*
17 *local protocols where the surgeon believes they will be of benefit (Grade D*
18 *recommendation).*

19 The benefit of early administration of tranexamic acid in reducing maternal mortality
20 has been proven in the WOMAN study. This is a large multi-centre, double-blind,
21 placebo controlled RCT comparing tranexamic acid to placebo to prevent death from
22 all causes of bleeding, including AIP and other morbidities⁶⁴(level 1b evidence).

23 Therefore, the IS-AIP recommendation for its use is as follows:

24 *Tranexamic acid should be administered whenever massive hemorrhage occurs,*
25 *preferably as soon as possible after onset of significant bleeding (Grade A*
26 *recommendation).*

27
28 *Surgical treatments*

29 *Internal Iliac Artery Ligation*

30 Four retrospective studies were identified reporting a total of 105 cases of internal
31 iliac artery ligation (IIAL) performed to reduce hemorrhage at deliveries complicated
32 by AIP⁶⁵⁻⁶⁸. Three of these were retrospective cases series of women undergoing
33 IIAL with no comparator group (level 4 evidence)^{65, 66, 68} and one was a retrospective

1 cohort study comparing outcomes for women with AIP treated with or without IIAL, at
2 the time of delivery (poor quality cohort, level 4 evidence)⁶⁷. The authors concluded
3 that IIAL did not contribute to a reduction in blood loss however, as the indication for
4 undertaking IIAL was not described, this study is highly likely to be confounded by
5 selection bias. Consequently, it was not possible to appropriately evaluate the
6 efficacy of IIAL for reducing blood loss.

7 *Uterine devascularization*

8 One retrospective study from Verspyck et al⁶⁹ reported immediate and long-term
9 outcomes in six women undergoing surgical uterine devascularization at the time of
10 cesarean followed by conservative management of their AIP (level 4 evidence). No
11 conclusion can be drawn from this regarding the efficiency of the technique for
12 hemorrhage control but the study demonstrated that uterine devascularization
13 appears to be a reasonably safe technique as long as it is not associated with
14 ovarian artery ligation.

15 *Uterine compression sutures*

16 Compression sutures after extirpation of placenta were reported in three
17 retrospective studies⁷⁰⁻⁷² including a total of 47 women. Shahin et al reported 26
18 cases of had bilateral uterine artery ligation followed by insertion of a B-Lynch suture
19 for major hemorrhage from AIP (level 4 evidence)⁷⁰. Two of the 26 women died.
20 Shazly et al reported a similar case series of seven women with hemorrhage from
21 AIP who underwent bilateral uterine artery ligation and then multiple compression
22 suturing (level 4 evidence)⁷¹. The authors reported that the procedure was
23 successful. For both these studies it is impossible to assess the efficacy of
24 compression sutures alone as the treatment also involved arterial ligation. The
25 absence of a control group makes it impossible to assess the efficiency of this
26 technique to reduce blood loss. Hwu et al reported a case series of 14 women who
27 had a vertical compression suture involving both the anterior and posterior uterine
28 walls to control bleeding from the placental bed (level 4 evidence)⁷². One of these
29 women was diagnosed with AIP. Again, there was no control group making
30 assessment of efficacy in reducing blood loss impossible.

31 *Balloon tamponade*

32 One retrospective study⁷³ compared first-line hysterectomy (17 women) and balloon
33 tamponade (19 women). Women who were assessed to have >50% invasion of the

1 axial plane of the uterus were treated with immediate hysterectomy. The remainder
2 had a balloon tamponade after extirpation of placenta with or without extra square
3 compression sutures to the placental bed. Blood loss and transfusion amounts were
4 significantly lower in the tamponade group ($p < 0.05$) however the selection criteria
5 used brings into question the appropriateness of the two groups (poor quality cohort,
6 level 4 evidence). Also, it was not clear if the tamponade was used to prevent or treat
7 hemorrhage. Three retrospective studies looking at treatment for PPH have also
8 reported that the presence of an AIP is associated with a higher failure rate of balloon
9 tamponade (level 4 evidence)⁷⁴⁻⁷⁶.

10 *Pelvic Tamponade*

11 A variety of techniques have been described for pelvic tamponade in the case of
12 persistent bleeding post-hysterectomy. Ghourab et al⁷⁷ described five cases of pelvic
13 packing with 10-12 dry abdominal swabs (level 4 evidence). Dildy et al⁷⁸ described a
14 case series spanning 38 years of pelvic packing using a variety of materials,
15 including pillow cases, gauze sheets, plastic X-ray cassette drapes and orthopedic
16 stockings, filled with gauze rolls (level 4 evidence). Charoenkwan et al⁷⁹ reported a
17 case series of three woman treated with pelvic tamponade using a large volume
18 Bakri balloon (level 4 evidence). There were no maternal deaths in any of the three
19 reports. No comment can be made on which technique provides the most effective
20 tamponade.

21

22 In light of the quality and potentially conflicting evidence available, the IS-AIP
23 recommendations for the surgical procedures to be used in case of massive
24 hemorrhage are mostly based on a consensus of expert opinion (level 5 evidence)
25 and are as follows:

26 *If the woman is stable, the bleeding is not imminently life-threatening and a*
27 *conservative approach was planned (either for maternal request or if hysterectomy is*
28 *anticipated to be at very high risk of surgical complications), surgical uterine*
29 *conserving procedures should be attempted before resorting to hysterectomy. The*
30 *simplest techniques with the lowest complications should be performed first (Grade D*
31 *recommendation).*

32 *If the placenta has been removed, intra-uterine tamponade (e.g. balloon tamponade)*
33 *should be the first line management. If this fails, or the placenta remains in situ,*

1 *uterine devascularisation, with or without uterine compressive sutures, should be*
2 *tried. Internal iliac artery ligation has the highest risk of post-operative complications*
3 *and therefore should only be performed if the previous steps have failed to control*
4 *the bleeding (Grade D recommendation).*

5 *If the woman is unstable or the bleeding is life-threatening, treatment must be*
6 *focussed on the source of the blood loss, this will most often be the placental bed, so*
7 *emergency hysterectomy should be performed as rapidly as possible. Vascular*
8 *compression (common iliac arteries or aorta) can be used as a temporary measure to*
9 *gain time to resuscitate the woman and complete definitive treatment (Grade D*
10 *recommendation).*

11 *In case of persistent pelvic bleeding following hysterectomy, internal iliac artery*
12 *ligation and/or pelvic tamponade should be considered. Pelvic tamponade should be*
13 *performed with appropriate, sterile equipment such as large abdominal swabs and*
14 *broad-spectrum antibiotics given whilst they remain in situ (Grade D*
15 *recommendation).*

16 **21. What is the likelihood of a further pregnancy for women who have had** 17 **an AIP and successful uterine conservation?**

18 Counseling women requesting uterine conserving treatment of AIP requires
19 knowledge of the evidence regarding the possibility of subsequent pregnancy and
20 associated risk of recurrence of AIP. There are case reports⁸⁰⁻⁸⁴ (level 4 evidence),
21 case series^{49, 71, 85, 86} (level 4 evidence), case-controlled⁸⁷ (level 3b evidence) and
22 cohort studies⁸⁸⁻⁹² (level 2b evidence) which clearly demonstrate preservation of
23 fertility after successful conservative management of AIP. There are however, no
24 prospective or randomized studies.

25 The largest cohort of 131 women who had successful conservative management of
26 AIP reported that 27 women expressed a desire for a subsequent pregnancy. Of
27 these, 24 women (89%) had 34 spontaneously conceived pregnancies (level 2b
28 evidence)⁹⁰. Another retrospective observational study assessed 46 women who had
29 successful conservative management of AIP⁹¹, 12 (86%) of the 14 patients desiring
30 another pregnancy achieved a total of 15 pregnancies (level 2b evidence). The only
31 other cohort study presenting outcomes for women desiring a subsequent pregnancy,
32 reported five out of six women (83%) achieved a successful pregnancy(level 2b

1 evidence)⁸⁸. These studies included women who had received a multitude of
2 additional treatments including administration of methotrexate, embolization of
3 uterine arteries, pelvic arterial ligation, hysteroscopic resection of retained tissues
4 and segmental excision of the uterus. No study addressed the effect that these
5 different management strategies had on fertility preservation or what degree of
6 placental adherence/invasion each woman had prior to conservative management.
7 Two of the cohort studies also examined the recurrence rates for AIP. In the largest
8 study⁹⁰, AIP recurred in 6 (29%) of the 21 pregnancies which continued beyond 34
9 weeks' gestation and was associated with placenta previa in 4 cases (level 2b
10 evidence). The other study reported that of the nine patients who delivered after 35
11 weeks' gestation, two (22%) had recurrence of placenta accreta (level 2b
12 evidence)⁹¹.

13 There is considerable evidence demonstrating that women who have successful
14 conservative management of AIP may go on to have a successful future pregnancy.
15 What remains unclear is what effect different methods used for conservative
16 management, such as arterial embolization or uterine resection, have on fertility rates
17 and what is impact the original degree of adherence or invasion. The IS-AIP
18 recommendation is based on the available evidence supported by expert consensus
19 (level 5 evidence) and is:

20 *Women wishing to preserve their fertility should be counselled that this is possible*
21 *(Grade B recommendation). If conservative management is successful, the*
22 *subsequent pregnancy rate is between 86% and 89% (Grade B recommendation).*

23 *There is no evidence regarding the association of AIP degree*
24 *(accreta/increta/percreta) or methods used for conservative management, and*
25 *successful preservation of fertility.*

26 *Women wishing for fertility preservation should be managed by a team with*
27 *appropriate resources and experience in conservative management according to that*
28 *team's local protocols (Grade D recommendation). These women should be*
29 *counselled that their risk of AIP in a subsequent pregnancy is between 22 and 29%*
30 *(Grade B recommendation).*

1 **DISCUSSION**

2 There were few questions that could be answered using high-level evidence, and
3 many of the recommendations are based on expert opinion. The paucity of
4 appropriate evidence for the optimal management of this difficult and potentially life-
5 threatening condition highlights the urgent need for large, multi-center collaborations.
6 However, until the international community comes to an agreement on robust clinical
7 diagnostic criteria and appropriate stratification of severity for AIP the issues with
8 comparing studies and translating research results into clinical practice will remain.

9
10 ***Acknowledgements:*** We would like to thank the past and present membership of the
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