

**ADVANCED ABDOMINAL PREGNANCY: diagnosis,
evaluation and surgical management in a resource
constrained setting.**



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DISSERTATION SUBMITTED TO THE UNIVERSITY OF
CAPE TOWN

In partial fulfilment of the requirements for:

Masters of Medicine in Obstetrics and Gynaecology

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of submission: 03 August 2019

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ACKNOWLEDGEMENTS

This dissertation is a tribute to my late mother, who passed away in a gynae ward, at Parirenyatwa hospital, Harare, in 1996, well before I pursued my medical career. I also acknowledge my late father who supported my big dreams.

I am grateful to my two boys for their love and selfless support.

I would like to acknowledge the following persons who contributed to the success of this research project;

- Dr N. P. Godi, who has been my mentor for the past 6 years, operated on most of these patients and under his guidance allowed me and other MOs to also operate on some of them.
- Prof L. M. Moja supported this project from its conceptualization and early ideas.
- Prof Sue Fawcus for being the perfect supervisor; I'm forever grateful.
- Ms Chiloane, the post natal ward (PNW) secretary who assisted with retrieving patient files from registry.
- Memory Mhembere for assisting with the data analysis.
- Dr Goosen for assisting with retrieval of RFH perinatal data at Mpumalanga DOH.
- Dr C. Jackson assisted with all HIV related queries in Ehlanzeni district.
- All colleagues at RFH who I worked with that took great care of these patients with inadequate resources.

Special mention goes to the patients who continue to trust Rob Ferreira hospital O&G unit for their health and that of their infants.

ACRONYMS AND ABBREVIATIONS

AP	Abdominal pregnancy
AAP	Advanced abdominal pregnancy
BP (mmHg)	Blood Pressure (millimetres of mercury)
Bpm	Beats per minute
BMI	Body Mass Index
CEO	Chief Executive Officer
CFR	Case Fatality Rate
CHC	Community Health Centre
CS	Caesarean Section
°C	Degrees Celsius
DOH	Department of Health
ENND	Early Neonatal Death
FFP/FDP	Fresh Frozen Plasma/ Fresh Dried Plasma
FM	Fetal movements
FSB	Fresh Still Birth
GA	Gestational Age
Hb (g/dL)	Haemoglobin (grams/decilitre)
HCU	High Care Unit
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
IOL	Induction of labour
IUFD	Intrauterine fetal death
LEC	Local Ethics Committee
MO	Medical Officer
MRI	Magnetic Resonance Imaging
PNW	Post Natal Ward
PPH	Post Partum Haemorrhage
PV	Per Vagina
RBC	Red blood cells
RFH	Rob Ferreira Hospital
SB	Stillbirth
SBP	Systolic BP
SI	Shock Index
SQL	Structured Query Language
UCT	University of Cape Town
USA	United States of America
USS	Ultrasound Scan
WHO	World Health Organization

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ABSTRACT

Introduction: Advanced abdominal pregnancy (AAP) is a pregnancy of over 20 weeks gestation, with a foetus living, or showing signs of having once lived and developed, in the mother's abdominal cavity. It is a rare obstetric complication associated with high maternal and perinatal morbidity and mortality. The question of whether to leave the placenta in or to remove it has been the subject of debate. When such cases present outside high resource settings, where a multi-disciplinary approach may not be possible, there are many challenges to effective treatment. The management of this rare but serious complication of pregnancy at Rob Ferreira Hospital (RFH), a rural provincial tertiary hospital, was investigated.

Methods: This was a retrospective observational study of patients with AAP identified from theatre registers from January 2011 to January 2018 at RFH. Data was collected on patient demographics, diagnostic challenges, preoperative evaluation, and surgical management particularly of the placenta, and outcomes. Delivery data for RFH was retrieved from the provincial database.

Results: There were 26 cases of AAP identified, for which 21 folders could be retrieved from the registry. The incidence of AAP was 66.2 per 100, 000 deliveries. Abdominal pain was a presenting complaint in 100% of patients. Ultrasound scan (USS) accuracy, prior to surgery, was eventually 90.5%. However, for 61.9% the diagnosis of AAP was missed at initial USS and for 33% of these, AAP was only diagnosed after failed attempts at induction of labour (IOL). AAP was diagnosed intra-operatively in 9.5%, for a supposed caesarean delivery and 19 (94.7%) were diagnosed pre-operatively. Intra-operatively, 36.8% patients had placental site bleeding for which partial placental removal was necessary in 71.4%. This group had more adverse maternal outcomes. For 73.7% of patients there was no bleeding from placental bed and the placenta was left in situ; but 7.1% required relook laparotomy for haemorrhage. There was one

maternal death. Overall neonatal survival rate was 14.3% and pregnancy loss rate was 71.4%.

Conclusion: This study shows that planned management of AAP in a resource constrained setting with tailored approach and management, can be performed without compromising maternal outcomes. However, poor outcomes occurred when pre-operative diagnosis was not made and AAP was discovered during emergency CS, emphasising the importance of antenatal diagnosis. USS and a high index of suspicion remains the best diagnostic tool. From this study it appears safe to leave the placenta undisturbed unless it can be safely removed, or the patient is already bleeding from the placental site. There were very low neonatal survival rates, and this needs to inform counselling of patients with AAP.

CHAPTER 1: INTRODUCTION

An ectopic pregnancy is one that implants outside the uterine cavity. A pregnancy beyond 20 weeks gestation outside the uterine cavity is designated an advanced abdominal pregnancy (AAP). Nkusu (2008) in a review of 163 cases defined AAP as a pregnancy of 20 weeks or more, with a foetus living, or showing signs of having once lived and developed, in the mother's abdominal cavity. AAP is very rare, such that only a few gynaecologists will encounter it in their professional careers. Patients with AAP and their babies are at risk of significant morbidity and mortality especially in resource constrained settings. Advances in technology and the introduction of early transvaginal ultrasound scan (USS) in routine antenatal care have enabled earlier diagnosis and definitive treatment of ectopic pregnancy, thus reducing the possibility of the condition progressing to AAP.

Rob Ferreira hospital (RFH) is a provincial tertiary hospital in Mpumalanga. Together with district hospitals in its health district, Ehlanzeni; it functions in a resource constrained setting. It lacks both experienced human resources and up to date technology. It cannot afford to offer routine antenatal USS to all pregnant women.

Surgical management of AAP in high resource settings involves a multi-disciplinary team that includes gynaecology, obstetrics, general surgery, vascular surgery, urology, haematology and interventional radiology. Devascularisation of placental vessels can be performed in such settings. When these cases present outside of such high resource settings, such as at RFH, there are many challenges to effective treatment. A major treatment challenge is whether to remove the placenta or leave it in situ. When these cases are diagnosed at RFH the definitive plan of management is elective surgery with detailed preoperative planning. The latter involves stabilising the mother, correcting anaemia, giving antenatal corticosteroids if indicated, and the surgery

is usually performed by the senior specialist gynaecologist or under his supervision.

1.1. Rationale for current study

AAPs are rare and are associated with very high morbidity and mortality. Discovering this type of pregnancy at a supposedly routine caesarean section (CS) compounds the associated morbidity and mortality especially in a resource constrained setting where appropriate surgical skill may not be available. The study will describe the overall management of this rare condition from case diagnosis through to outcomes with a focus on what can be achieved in low resource settings without a multidisciplinary team. Findings from the study are likely to bring awareness to medical personnel working in similar settings to RFH about managing this rare condition. It may also provide recommendations on optimal management and enable resource re-allocation in order to improve management of this condition.

CHAPTER 2: LITERATURE REVIEW

Databases were searched for articles on AAP. Most are retrospective case studies with no randomised controlled trials of management. Studies were reviewed from different geographical regions and settings, some similar and others very different to the setting of this study. Older versus newer literature is described to give an overview of the changing trends in the incidence and management of AAP. Most of the settings described are urban teaching hospitals which tend to be better resourced than rural tertiary hospitals such as RFH.

2.1. General background:

The site of implantation of most ectopic pregnancies is the ampullary region of the fallopian tube. Abdominal pregnancy (AP) is estimated to constitute 1% of all ectopic gestations (Nwobodo 2004). It is an implantation in the peritoneal cavity exclusive of tubal, ovarian, or intraligamentous implantations (Cunningham 2014). AP can rarely be a primary peritoneal implantation but mostly it is a secondary implantation. The latter follows tubal pregnancy rupture or abortion which then re-implants in the peritoneal cavity. Yahia (1956) describes 2 of their 8 cases as primary APs; six were secondary APs, in one of which the primary site was thought to be the right ovary. The other 5 were thought to be earlier tubal ruptures. In cases of AAP, it is not unusual, for the placenta to be at least partially, attached to the uterus and adnexa (Cunningham 2014).

AAP is associated with high maternal and perinatal morbidity and mortality. This is due to associated haemorrhage, sepsis and injury to other pelvi-abdominal organs. Haemorrhage can occur pre-, intra- and post-operatively. Intra-operative bleeding is usually related to the surgical management of the placenta. In AAP, the placenta is embedded on pelvi-abdominal structures and derives its blood supply from, the uterus, adnexa, bowel, omentum, bladder, and posterior abdominal wall. The placenta can also be found attached to higher up abdominal

organs, such as the liver and spleen and also the anterior abdominal wall (White 1989). The usual mechanism of uterine contraction which obliterates the large spiral arteries in an intrauterine pregnancy is absent. When the placenta is removed, or the placental bed is disturbed massive haemorrhage can follow from the large maternal vessels supplying it. In removing an extrauterine placenta all these blood vessels supplying the placental bed would have to be ligated.

The bleeding is exemplified by Amal (2011) in a case report from the Maternity and Children hospital, Jeddah, Saudi Arabia, at surgery for a supposed CS. Massive bleeding followed removal of the placenta. They had to resuscitate with a total of 4000mls of crystalloid, 7 units of packed red blood cells (RBC), 4 units of fresh frozen plasma (FFP), 10 units of cryoprecipitate and 2 units of platelets. Despite these aggressive efforts the patient continued to bleed. They eventually gave 90 units/kg of factor VII to control the bleeding.

2.2. Incidence

The incidence of AAP varies mainly because there is no universal agreement on the definition of “advanced”. Yahia (1956) designated AAP to any gestation outside the uterine cavity of 5 months duration or more. They describe 8 such patients among 68,394 deliveries at Sloane hospital for women, Columbia University, New York, with an incidence of 11.7 per 100, 000 (1 in 8,550) deliveries. Rahman (1982) reported 10 AAPs, an incidence of 9.8 per 100, 000 deliveries over a 10-year period at King Faisal University hospital in Saudi Arabia. They described patients who were in the third trimester of their pregnancy except one at 22 weeks who had a heterotopic pregnancy.

Atrash (1987), from the Centres for Disease control and Prevention, estimated that in the United States, there were 10.9 APs per 100,000 live births and 9.2 per 1000 ectopic pregnancies. Whereas Atrash estimated the incidence of all AP, Worley (2008) focussed on AAP using a case definition of 18 weeks or more. They

reported a series of 10 patients at Parkland hospital, Dallas, Texas, over twenty-five years and reported an incidence of 4 AAPs per 100, 000 births. From older literature, Dixon (1960) at Jamaica University College hospital, described 10 AAPs over 6 years, using a case definition of 20 weeks or more, among 9,303 deliveries, giving an incidence of 107.5 per 100,000 deliveries. At Harare hospital, Zimbabwe, White (1989) describe 23 patients who were 20 weeks and over, during a 10-year period, an incidence of 10.5 AAP per 100, 000 (1 in 9500) deliveries and 1 in 60 ectopic pregnancies. At Baragwanath hospital, in Soweto, Johannesburg, Golan (1985) observed 43 patients with AAPs using a case definition of more than 34 weeks gestation; an incidence of 15.7 per 100, 000 (1 in 6389) deliveries. The wide variation in incidence estimates for AAP could also be due to the nature of the denominator used and whether it was population or facility based.

AAP is thought to be less common in high than low resource settings. Edmonds (2012) believes that as accuracy and availability of first trimester transvaginal USS in well-resourced settings increases, the prevalence of AAP will decline further. It is recommended that all pregnant patients book in the first trimester and USS is performed to locate the pregnancy. If they are found to have an ectopic pregnancy and are managed appropriately, this avoids progression to AAP and its associated morbidity and mortality.

2.3. Diagnosis

The diagnosis of this condition should still follow the usual tenets of clinical evaluation, encompassing history, examination and special investigations. As King (1954) pointed out, the diagnosis is often missed simply because this rare condition is not considered. From experience in Natal, South Africa, Suren (1998) said a high index of suspicion is necessary. Ombelet (1988) at St. Jan's Hospital, Genk, Belgium, in their description of 38 cases, emphasized the marked differences in clinical symptoms in presentation of patients. They described three

typical cases; the first was referred for induction for suspected intrauterine foetal death (IUFD), the second had an intraligamentous pregnancy with a living foetus and the third patient was admitted to hospital after 32 weeks for persistent oblique lie. One of the patients in the series at Chris Hani Baragwanath hospital, Soweto, South Africa had been admitted for a hysterectomy for a large fibroid uterus; she was then found to have had a full-term calcified AAP for 5 years (Golan 1985).

2.3.1. Symptoms

AAP should be suspected in patients with persistent abdominal pain in late pregnancy and those who complain of painful foetal movements (FM). Rahman (1982) reported that the most frequent symptoms were abdominal pain (100%), nausea and vomiting (70%), general malaise (40%) and painful FM (40%). At Baragwanath hospital, abdominal pain and vaginal bleeding were the most common complaints (Golan 1985). Dixon (1960) reported a history of “spurious” labour at or near term in three of their patients. Vaginal bleeding in early gestation was noted in 87% of patients reported by Yahia (1956).

2.3.2. Signs

Abnormal foetal positions maybe palpated in AAP, but ease of palpating foetal parts is not a reliable sign (Edmonds 2012). In the review from Harare hospital abnormal presentation of the foetus, displacement of cervix and anaemia were common features (White 1989). Common physical findings described by Rahman (1982) were abdominal tenderness (100%), abnormal foetal lie (70%) and a displaced cervix (40%). Golan (1985) states that vaginal examination with a displaced firm long cervix, contributed to diagnosis in the majority of their patients.

2.3.3. Ultrasound

Ombelet (1988) emphasized that USS was the most useful diagnostic technique in AAP. Suren (1998) also mentions that USS is the best investigative tool.

However, even in ideal conditions, a diagnosis of AP by USS is missed in half the cases (Costa 1991; Worley 2008). In Worley's series, of the 5 out of 10 patients missed by USS, one was diagnosed as a total placenta praevia. Edmonds (2008) notes that clinical suspicion of AAP should be followed by a transvaginal scan to establish continuity between cervical canal, uterine cavity and gestational sac.

Also, APs that progress beyond the first trimester are typically missed on routine transabdominal USS. It is often difficult to obtain clear images of the foetus due to overlying bowel loops. Evidence of oligohydramnios and early growth restriction frequently occur in AAP. In addition, diagnosis of foetal demise on USS may not prompt to detect the fact that maybe the pregnancy is extra-uterine.

2.3.4. Other diagnostic aids

Failure to induce contractions during oxytocin infusion for suspected IUFD was mentioned by Hertz et al (1977) as an important diagnostic test. Golan (1985) used the 'oxytocin test' in 35 of their patients. Failure to induce labour with other methods including prostaglandins, plain abdominal radiographs, and magnetic resonance imaging (MRI), are also mentioned as additional diagnostic tools in the literature.

In summary, presentation of AAP can range from being asymptomatic to acute abdominal pain with hypovolemic shock. It can then be confused with other diagnoses including ruptured uterus, and placenta abruption.

2.4. Management of AAP

Surgery is always necessary for AAP ideally in a tertiary centre with a multi-disciplinary team.

2.4.1. Patient counselling

When a diagnosis of AAP is made, patients require extensive counselling; about the maternal and perinatal risks associated with AAP and management options. This aspect of care is not well described in reviewed literature.

2.4.2. Timing of the operation

In haemodynamically unstable patients, surgery is urgent and needs to be performed in the hospital where the woman presents. If the patient is stable, there is time for elective transfer to a tertiary care facility. If the foetus is alive it is more difficult to decide on the timing of surgery, than if it has already died; delaying it could allow the foetus to achieve lung maturity but postponing it could mean that the clinical condition becomes a surgical emergency. Beck (1919) thought there was little additional risk in delaying operation until the 38th week in the hope of obtaining a live child. Recently some recommend administering antenatal corticosteroids and waiting until foetal viability at 28 weeks with hospital observation if the pregnancy is diagnosed after 24 weeks (Cartwright 1986; Hage 1988). An alternative end-point would be foetal lung maturity at 34 weeks. Dixon (1960) delayed operation in one of their patients, after diagnosis at 30 weeks with a successful outcome. The patient was kept in hospital and delivered at 35 weeks.

2.4.3. Surgical management

Careful pre-operative planning is essential to ensure all relevant specialists are available and there are sufficient supplies of blood products on site. As already mentioned, this may be limited when the condition is diagnosed inadvertently at emergency CS or in a rural regional hospital where there are limited numbers of specialists.

The surgery involves delivery of the foetus which may be alive or dead. Subsequent management all hinges on the site of attachment of the placenta

and whether there is already bleeding from partial or total detachment. In general attempts to remove an undisturbed placenta may be associated with massive bleeding; whereas leaving it in situ may be associated with post-operative morbidity and sepsis.

At Harare hospital, White (1989) described the perioperative course of a total of 23 patients with AAP. The placenta was left undisturbed in 13 patients, and partially or totally removed in 10. The reasons for attempting placental removal were not described. They commented on greater blood loss and haemodynamic instability in those in whom placenta removal was attempted. However, the patients who had some placental tissue left had a far more prolonged hospital stay averaging 27.4 days (6-63 days) in comparison to 8.3 days for those with the placenta removed completely. In their series, one patient stayed in hospital for 63 days, and four required relook laparotomy, two for intestinal obstruction and two for a painful abdominal mass. None of their patients died.

In the series by Golan (1985) of 43 patients, from Baragwanath hospital, the placenta was attached to uterus, adnexa, broad ligament in 18 patients (42% of 43), bowel and omentum in 12 patients (28% of 43) and was peritubal in 8 patients (18% of 43). In the remainder it was attached to the abdominal wall, and the bladder, or it was found free in peritoneal cavity. It was removed without damage to these critical neighbouring structures in 93% of cases but they report excessive haemorrhage in all. Four patients required hysterectomy and there were two maternal deaths. The first patient who died had prolonged surgery, severe haemorrhage; and multiple packing after the placenta was removed. She then developed peritonitis and died after surgery. The second patient died during intra-amniotic saline IOL for a supposed IUFD. Golan, based on this series, recommends leaving the placenta in situ unless it can be removed safely and that the patients should receive appropriate prophylactic antibiotic cover.

Dixon (1960) reported 10 patients with AAP, for whom the placenta was removed. Nine out of the 10 patients required further surgery; six had hysterectomy and unilateral salpingo-oophorectomy was done in three. All had an uneventful recovery postoperatively.

The majority opinion from older studies favours leaving the placenta in situ, except in cases when it is so situated that it can be removed safely and easily (Dixon 1960). The case series by Yahia (1956), reported no maternal deaths among their eight cases. The placenta was removed entirely in six patients with AAP. In one of their patients, the placenta was left in situ when attempts to remove it were met by significant haemorrhage. They had to pack the abdomen to tamponade bleeding. The patient required relook laparotomy at 1 month and subsequently in 2 years. At the last operation she had a hysterectomy, right salpingo-oophorectomy, enterocutaneous fistula excision. Yahia (1956) concludes that the remote need for relook laparotomy because of sepsis does not outweigh the significant risk from catastrophic haemorrhage.

More recently, Edmonds (2012) and Cunningham (2014) suggest that at surgery, the gestational sac should be carefully opened avoiding disruption of the placenta, the foetus removed, cord cut short and the placenta left in situ. They describe this approach as the 'lesser of two evils' and decreases the chance of immediate life-threatening haemorrhage.

Placental removal (Cartwright 1986; Delke 1982; Hallatt 1985) is necessary if there is already haemorrhage from its implantation site. Cunningham (2014) noted however, that leaving the placenta in situ is also associated with severe morbidity. They quote Bergstrom (1998) and Martin (1988) who reported that when left in the abdominal cavity the placenta commonly becomes infected with subsequent formation of abscesses, adhesions, intestinal obstruction and wound dehiscence.

In the 10 patients from Parkland hospital, Dallas, Texas, United States, described by Worley (2008), the placenta was left in situ in two patients who developed major morbidity from severe sepsis syndrome, requiring further laparotomies and prolonged hospital stay. Rahman (1982) also reported higher postoperative morbidity and mortality when the placenta was left in situ.

2.4.4. Summary of surgical management of placenta:

In summary, it appears from the literature described that the correct surgical approach needs to be tailored to operative findings (where the placenta is implanted and whether there is any placental site bleeding) and available specialist skill. There are advantages and disadvantages to both courses of action, notably placental removal or leaving it undisturbed. It appears most practitioners agree that the placenta should be left undisturbed unless it can be safely removed; notwithstanding the sepsis risk from this approach, removing the placenta partially is the most dangerous. Safe removal depends on a number of variables including surgical skill, advanced anaesthesia skill, placenta attachments, and placental blood supply. In the presence of hypovolaemic shock with the placenta already partially or totally detached, the surgeon has no choice about placental removal and operative measures to secure haemostasis become the focus of surgery.

2.5. Maternal mortality and morbidity

The case fatality rate (CFR) for AAP was 5.1 per 1000 in the Atrash (1987) estimates, nil in the Yahia (1956) and Dixon (1960) series and 46.5 per 1000 in the Golan (1985) series. Severe morbidity in AAP as evidenced by the need for hysterectomy occurred in 62.5% patients (Yahia 1956), 45% (Beacham 1962), 60% (Dixon 1960) and 9% (Golan 1985). HIV did not seem to worsen morbidity in the three patients reported by Leyva (2011). They reported no mortality and no significant morbidity. Placenta resorption was complete at follow-up

sonography in the one patient it had been left in situ. The placenta was removed completely in two patients.

Clark (1975) in their series of advanced ectopic pregnancy at Freedman's hospital, Washington D. C. USA; they concluded that removing the placenta is associated with much lower morbidity, but the mortality rate is higher. However, they reported no maternal deaths and in their series the placenta was only left intact in three patients. They also do not describe the kind of morbidity suffered by those with placenta removed in comparison to those in whom placenta was left intact. When Stevens (1993) reviewed reported literature from 1809 maternal mortality declined from 30.7% (102/332) prior to 1933, to 14.6% (38 of 260) between 1934-1950, 9% (11 of 122) from 1951-1970 and 4.5% (7 of 154) in the period 1971-1990. She concluded that this was due to appropriate preoperative planning. The case fatality rate thus reduced from a mean of 182 per 1000 to 45 per 1000 in the past 20 years.

2.6. Perinatal morbidity and mortality

The foetuses are usually found either lying freely among pelvi-abdominal organs with little liquor amnii around them or are completely covered with a thin or thick membrane in a gestational sac. The usual protective intrauterine environment and the normal adaptive changes from implantation, including a sufficient amount of liquor for foetal growth and development is absent in an extrauterine pregnancy. It would thus be expected that pulmonary hypoplasia and limb deformities are common because of space constraints and the associated oligohydramnios.

In the series of 43 AAP cases by Golan (1985) in Baragwanath hospital, 25 were SBs, 10 ENND, 8 were discharged alive, giving a pregnancy loss in women with AAP of 81.4%. All patients described by Golan were above 34 weeks. Of 43 described in their series, all those born under 2000g were SBs. All survivors had

minor pressure deformities. Five had major malformations; talipes equinovarus in 3, myelomeningocele and one with severe asymmetry of skull and face. Stevens (1993) in the review of literature mentioned already described survival of infants born alive at 30 or more weeks. It improved from 54.6% prior to 1933, to 70.2% (1934-1950), 73.7% (1951-1970) and 78.3% from 1971-1990; a mean survival rate of 63% of cases. The malformation and deformation rates were just over 21%. Facial and/ or cranial asymmetry and joint abnormalities were the most common.

In their analysis of 163 cases of AAPs, from 13 countries since 1946, Nkusu (2008) reported a pregnancy loss in women with AAP of 72%. Pressure deformities of face, skull and limbs were common among the 18% of survivors. They also had congenital abnormalities, with 5 having more serious anomalies. In the report from Harare hospital, by White (1989), only 5 out of the 23 were born alive. One died shortly after due to pulmonary hypoplasia and four had multiple pressure deformities. Their pregnancy loss in women with AAP was 83%.

With such high maternal and perinatal mortality ranging from 2 to 18% and from 75 to 95% respectively (Delke, 1982; Hallat, 1985) it becomes challenging to counsel the mother with regards to outcomes.

CHAPTER 3: AIMS AND OBJECTIVES OF THE STUDY

3.1. Research Question

What are the diagnostic challenges, surgical management and outcomes of patients with AAPs, managed at RFH?

3.2. Study aim:

The aim of this study was to describe the clinical presentation, surgical management and outcomes in patients with AAP presenting to a rural provincial tertiary hospital.

3.3. Study objectives:

- To describe the different clinical presentations in terms of symptoms and signs.
- To describe how the diagnosis of AAP was made.
- To describe the surgical procedures performed for each case of AAP.
- To describe the perinatal and maternal morbidity and mortality.

CHAPTER 4: METHODOLOGY

4.1. Study design

It was a retrospective observational study in which patients with AAP managed at RFH between January 2011 and 2018 were analysed.

4.2. Study site

The Study was performed at RFH. It is a rural provincial tertiary hospital that serves Ehlanzeni district in Mpumalanga as both a regional and tertiary referral facility. It is a referral hospital for district hospitals, regional hospitals and several CHCs in this rural district, located in Nelspruit. Mpumalanga is one of the most economically disadvantaged provinces of South Africa with limited resources. RFH thus serves a predominantly low socio-economic status, historically disadvantaged black population. It is poorly resourced in both equipment and experienced medical professionals. It has 2 full time Obstetricians and Gynaecologists. Approximately 4500 women deliver at RFH annually. From January 2011 there was improvement in documentation of theatre cases with separation of obstetrics and gynaecology cases from other disciplines and the registry moved to a new site.

Routine early pregnancy USS is not offered at RFH, referring hospitals or clinics in its catchment area due to the lack of equipment and/or trained human resources. The majority of patients do not get a single USS in their pregnancy. The few who get an early transvaginal scan are those who present with early pregnancy complications. RFH has developed its own care policy for managing women with AAP as follows:

4.2.1. The RFH approach to managing AAP:

This approach has evolved by experience over the last twenty years. Elective surgery is planned for all patients by the senior specialist, unless they are haemodynamically unstable. Pre-operatively, an USS is performed by the senior specialist usually the day before elective surgery to ascertain the position of the placenta and the relative position of the foetus. An impression of whether the foetus is lying freely in the abdominal cavity or in a gestational sac is made. The incision is planned to avoid the placenta as much as possible.

Patient counselling at RFH: Counselling is by the most senior member of the team. Patient is informed of the diagnosis, diagnostic accuracy of procedures performed and the associated materno-foetal risks and outcomes. Surgical intervention, complications of surgery, preparation and timing is then discussed.

Surgery: After abdominal entry the abdomen is inspected; noting the presence or absence of a gestational sac. The area of least vascularity on the gestational sac is found and opened usually using diathermy to extend it. If no gestational sac, usually omentum is just reflected to reveal the foetus and placental mass. The foetus is delivered as gently as possible. The umbilical cord is tied at its insertion on the placenta, with absorbable suture. Tugging on the cord and disturbing the placental bed is avoided as much as possible. The abdomen, placenta and the sac are inspected for bleeding; then rinsed with small amount of saline. The placental attachments are not extensively evaluated but the obvious attachment to abdominal wall, omentum, bowel adhesions, uterus and adnexa is recorded in the notes. Placental site bleeding is managed with haemostatic sutures or placental removal when necessary to control bleeding.

Postoperative care: Patients are admitted to ICU, a labour ward High Care Unit (HCU), or straight to PNW depending on the difficulty of surgery and anticipated haemodynamic instability. A broad-spectrum antibiotic is given routinely; 3 or 9

doses of cefazolin, depending on HIV status. Danger signs and advice on when to return is given on discharge; usually day 3. There is no routine follow-up of this group of patients.

4.3. Study subjects

4.3.1. Inclusion criteria

The study subjects were all patients diagnosed with AAP (gestational age ≥ 20 weeks) at RFH. Patients in whom the diagnosis was suspected and/or initially managed at district hospitals and referred for complications were included.

4.3.2. Exclusion criteria

Patients with extra-uterine pregnancy before 20 weeks were excluded.

4.3.3. Identification of cases

Patients with AAP were identified from the RFH theatre register and maternal mortality meeting data. Patient files of the identified patients were then retrieved from RFH registry.

4.4. Data collection and analysis

4.4.1. Data collection

A purpose designed data collection sheet on excel was used to capture data. Data was collected on patient demographics, clinical presentation and diagnosis of AAP, preoperative evaluation, surgical management, and maternal/ foetal outcomes.

Perinatal data on total deliveries at RFH for the same time period was retrieved from Mpumalanga provincial department of health database. This was used to estimate the incidence of AAP.

4.4.2. Data analysis

Data was analyzed using R version 3.5.1 (Feather spray) Microsoft Structured Query Language (SQL) and a statistician assisted with data analysis. Frequencies and percentages were calculated for each variable. Since AAP is a rare condition, the numbers of patients were too few to perform comparative analyses which would achieve statistical significance.

4.5. Ethics

The research was a retrospective study and only used information extracted from patient files. Therefore, no individual patient consent was required. Patient details were not disclosed, and all data was kept securely. Approval was obtained from RFH Chief Executive Officer (CEO) and Mpumalanga local ethics committee (LEC) for access to the patient records. The protocol was approved by Human Research Ethics Committee University of Cape town (HREC REF 482/2018). See Appendix.

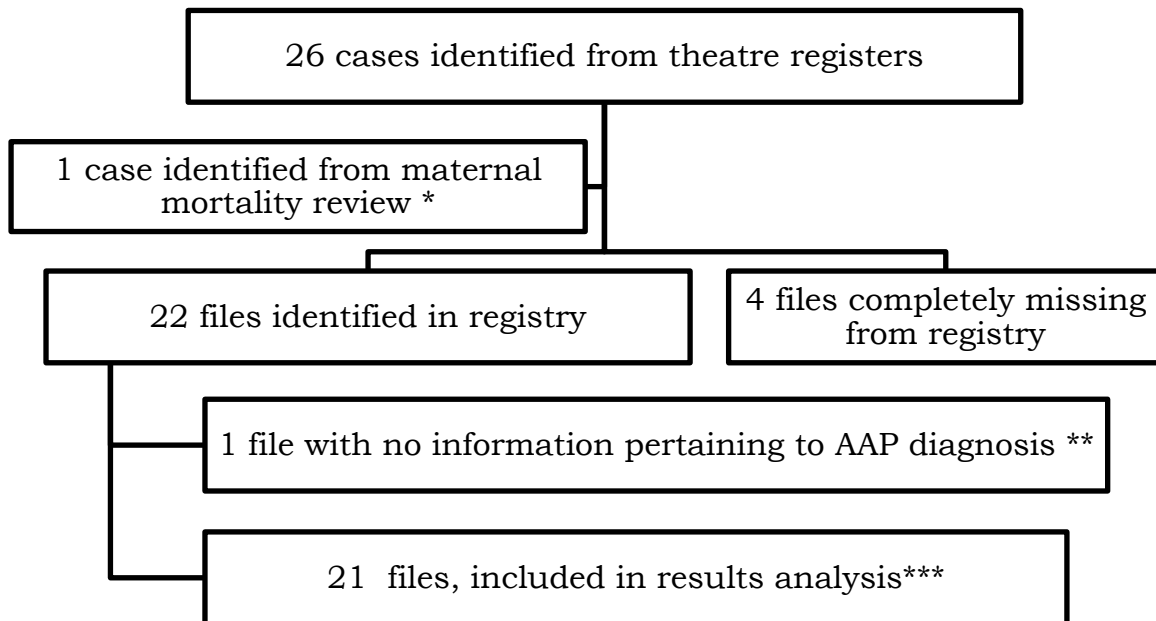
CHAPTER 5: RESULTS

5.1. Case identification

There were 26 patients with AAP identified from theatre registers, one of which was also identified from the maternal mortality review meeting minutes. Four files could not be found in the Registry and one had all the data relating to the AAP missing. This meant that a total of 21 patient files were included in the results analysis. Some of these had missing information for some variables and this is denoted in the results tables that follow.

The total deliveries at RFH over this seven-year time period was 31,717, giving an incidence of AAP of 66.2 per 100, 000 (1 in 1510 deliveries), and a mean of 3 cases per year.

Figure One: Identification of study patients with AAP



* Already found from theatre records

**Patient file found but did not contain notes pertaining to AAP management.

*** Included two files with incomplete data; operative details missing

5.2. Socio-demographic and clinical characteristics

Table 1 describes the socio-demographic data and clinical features of the study group. Data for several parameters were incomplete due to the relevant information not documented in the folder. There were no teenagers diagnosed with AAP and only one patient was in her forties. The age range was 20 to 43 years, with mean age of 30 years and the median parity was 1. Of the fourteen booked patients with documented gestational age, 11 (78.6% of 14) booked in the second trimester, one (7.1% of 14) booked in the first trimester and two (14.3% of 14) booked in the third trimester. Nineteen of the patients diagnosed with AAP, had known HIV status, with 15 (78.9% of 19) HIV positive. Data was not retrieved on HIV treatment status or the level of immunosuppression. Two thirds of patients, 8 (67% of 12) with recorded Haemoglobin (Hb) were already anaemic (Hb<10g/dL) when they booked. There was no patient with previous surgery for ectopic pregnancy.

Table 1: Demographic and clinical factors

Variable*	Mean (range) or n (% of N)
Age (years)	30 (20-43)
Parity	1 (0-4)
Gravidity	2 (1-5)
Booking Gestational Age (GA)** (weeks)	17 (12-30)
Booking Body Mass Index (BMI)	25.3 (18.5-33)
Booking Hb (g/dL)	9.8 (7.2-12.9)
Previous caesarean section	2 (9.5% of 21)
HIV status	
Positive	15 (78.9% of 19)
Negative	4 (21.1% of 19)

* N=21 for all parameters, except BMI (N=10), booking Hb (N=12), Booking GA (N=14) and HIV status (N=19)

**15 booked, 2 unbooked, 4 unknown, booking GA only known for 14.

5.3. Clinical presentation

5.3.1. Symptoms

Only 19 patients had adequate antenatal records. The majority of patients, 16 (84.2% of 19) with AAP, had consulted with a health practitioner on one or more occasions prior to eventual diagnosis, complaining of symptoms detailed in Table 2. The number of times they presented ranged from two to five times before the diagnosis was made. The symptoms described in the table include all presentations in the antenatal period, including the episode when the diagnosis was made. All 19 (100% of 19) patients presented with abdominal pain. In 3 (15.8% of 19) of the patients, the abdominal pain was associated with FMs. Reduced FM were a symptom in 12 (63.2% of 19) of the patients. Absent FMs were reported in 8 (42.1% of 19) and vaginal bleeding reported by 5 (26.3% of 19) patients. No patients presented with complaints of dizziness or fainting.

Table 2: Symptoms

Symptom	No. of patients (N=19) *	Percentage (%)
Abdominal pain	19	100%
Abdominal pain with FM**	3	15.8%
Reduced and/ or absent FM	12	63.2%
PV bleeding	5	26.3%
Nausea & vomiting	5	26.3%
Constipation	3	15.8%
Diarrhoea	2	10.5%

* Symptoms unknown in 2 patients.

** Fetal Movements

5.3.2. Signs

The Shock index (SI), [Heart rate (HR) /Systolic Blood Pressure (SBP)] was used to evaluate haemodynamic stability of patients at presentation when the diagnosis of AAP was made. Both SBP and HR measurements at diagnosis were recorded in 16 patients. Using Nathan's interpretation of SI (Nathan 2015), 11 (68.75% of 16) patients were haemodynamically stable (SI <0.9), 5 (31.25% of 16) had signs of early shock (SI >0.9<1.7), and there were no patients with severe life-threatening shock (SI>1.7). Although one patient, who was sent back from the district hospital, had haemodynamic instability before surgery, she had been stable at initial diagnosis of AAP, before being down-referred to a regional hospital for expectant in-hospital observation. Hb at diagnosis was known for twenty patients and ranged from 4.4 to 11.6g/dL, with the mean Hb being 9.1g/dL. Recorded temperature ranged from 35.4-38.3°C with a mean of 36.6°C.

Table 3: Vital signs at Diagnosis

	No of patients (N=16)	Percentage, (mean; (range)
SI <0.9	11	68.75%
SI >0.9<1.7	5	31.25%
SI >1.7	0	0
**Hb (g/dL)	20	9.1 (4.4-11.6)
Temperature (°C)	15	36.6 (35.4-38.3)

*HR and SBP both recorded in 16 patient files at diagnosis.

**Hb recorded in 20 files.

Table 4: Physical signs

Sign	No. of patients (n=20) *	Percentage (%)
Abdominal tenderness	13	65%
Abnormal fetal lie and/ or presentation	7	35%
Cervical motion tenderness	2	10%
Cervix displaced	2	10%
Easily palpable fetal parts	1	5%
Absent fetal heart	8	40%

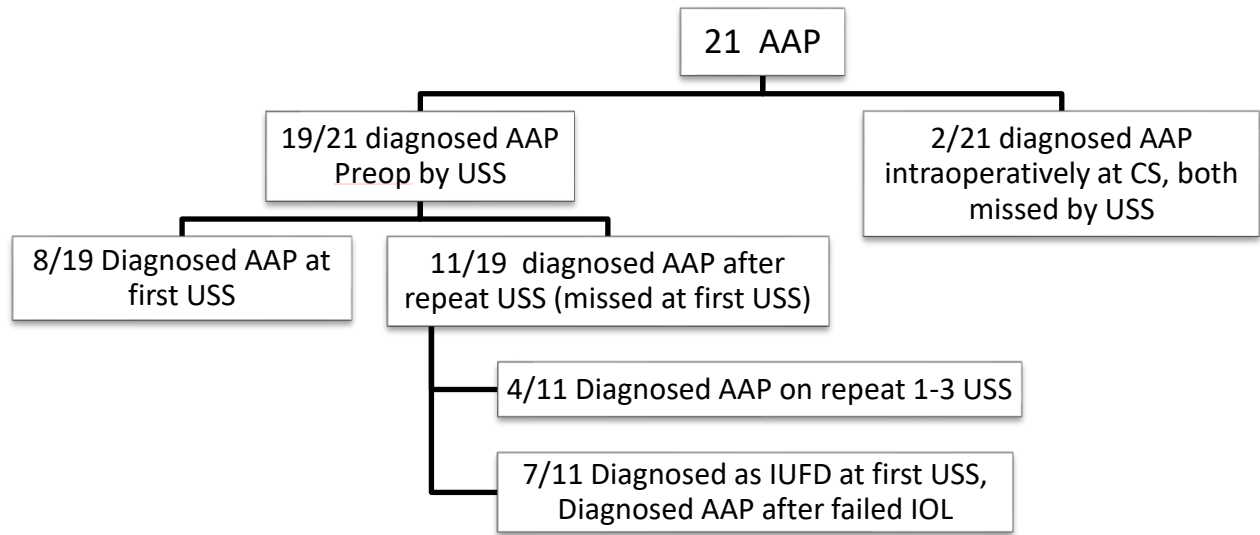
*Data missing for 1 patient.

Physical examination was normal in 7 (35% of 20) patients with AAP. For those with signs, the most common findings were abdominal tenderness, abnormal foetal lie and/or presentation and an absent foetal heart activity in 13 (65% of 20), 7 (35% of 20) and 8 (40% of 20) respectively. See Table 4

5.4. Method of diagnosis of AAP

The method of diagnosis of AAP is depicted pictorially in Figure two below. Over ninety percent, 19 (90.5% of 21) of patients were diagnosed as AAP pre-operatively by USS. However, the diagnoses of AAP were made at first USS in only 8 (38.1% of 21) patients and after 1 to 3 repeat USSs in 11 (52.3% of 21). These 11 patients included seven for whom the initial USS diagnosed an IUFD and AAP was only diagnosed subsequently after failed IOL. Of note, 13 (61.9% of 21) patients had an initial USS that missed the diagnosis of AAP.

Figure two: Diagnosis of AAP



Half, 4 (50% of 8) of the initial USSs that made the diagnosis of AAP were done at RFH. District hospitals contributed strongly suspicious scans in 3 (37.5% of 8) patients and 1 (12.5% of 8) patient were from a private general practitioner. Diagnosis was then confirmed at RFH. Seven (87.5% of 8) of initial USSs that diagnosed AAP were done in the third trimester, ranging from 28 to 38 weeks. Only one (12.5% of 8) of the initial diagnostic USSs were done in the second trimester.

Two (9.5% of the 21) patients had the diagnosis of AAP made during surgery for a supposed CS. Both had had at least 3 USS that failed to make the diagnosis of AAP. The first patient was taken to theatre for CS as a persistent breech with supposed fibroid at a district hospital. At surgery, AAP was diagnosed, and the baby delivered. Attempted removal of the placenta led to uncontrollable haemorrhage and she was transferred to RFH for relook laparotomy. The second patient was admitted to RFH as acute pyelonephritis at 34 weeks. She had had an USS at 29 weeks that assessed her pregnancy as intrauterine. An USS performed to assess growth while she was admitted, diagnosed an IUFD. Repeat

USS after failed IOL by a medical officer suggested AAP, but the specialist diagnosed complete placenta praevia with IUFD and planned CS.

Seven (53.8% of 13) of initial scans that missed the diagnosis of AAP were performed at the district hospitals, 5 (38.5% of 13) patients had these scans at RFH and one (7.7% of 13) was done by private practitioner.

5.5. Timing of the operation

Elective surgery could be planned for 19 (90.5% of 21) patients with AAP because their diagnosis was known prior to surgery. Despite having signs of early shock in 5 (31.25% of 16) patients, surgery was planned to be elective in all 19 (100% of 19) patients diagnosed pre-operatively after adequate resuscitation where necessary. Those who also had anaemia were optimized with transfusions and fluid resuscitation before surgery. One (5.3% of 19) of these patients had to be operated as an emergency for signs of suspected intra-abdominal haemorrhage that developed during expectant management.

Surgery was delayed for a variety of reasons. Delay was up to 48 hours for five (26.3% of 19) patients requiring blood transfusion and for eight (42.1% of 19) patients for experienced staff to be available, because the diagnosis was made after working hours. Surgery was also delayed in 7 (36.8% of 19) patients to improve foetal lung maturity. These seven patients were diagnosed between 28w0d and 33w6. They were all given a 48-hour course of steroids before surgery. Some patients had more than one reason for delay of surgery. For two (10.5% of 19) patients' surgery was planned to be delayed electively after discussion with the patient to try and improve foetal outcome up to 2 or more weeks; the first patient was diagnosed at 26 weeks with a live foetus. Surgery was delayed for two weeks to 28 weeks with hospital observation and steroids at RFH. The baby, however, was severely dysmorphic with lung hypoplasia and demised a few hours after delivery. The second patient was diagnosed with AAP

at 28 weeks with a live AAP and adequate liquor. A plan was made to defer surgery to 34 weeks and she was down referred to a regional hospital for this time period. However, two days later she developed intra-abdominal bleeding and severe haemorrhagic shock and had to be transferred back to RFH for emergency laparotomy. There was a haemoperitoneum of 3 litres, the baby was a fresh stillbirth and haemostasis was achieved with difficulty.

5.6. Operative details

5.6.1. Expertise of surgeon

The same senior specialist surgeon conducted or assisted with the surgery in 18 (94.7% of 19) of the patients with AAP diagnosed pre-operatively; in 17 he was present from the outset and in one he was called to assist by the medical officer (MO) who had commenced the surgery. The 19th patient had surgery performed by another gynaecologist. For the two patients discovered to have AAP at caesarean sections, both operations were commenced by MOs, one at RFH who called the specialist and the other at a district hospital who closed the abdomen and referred the patient to RFH for relook laparotomy which was performed by the senior specialist

5.6.2. Abdominal entry

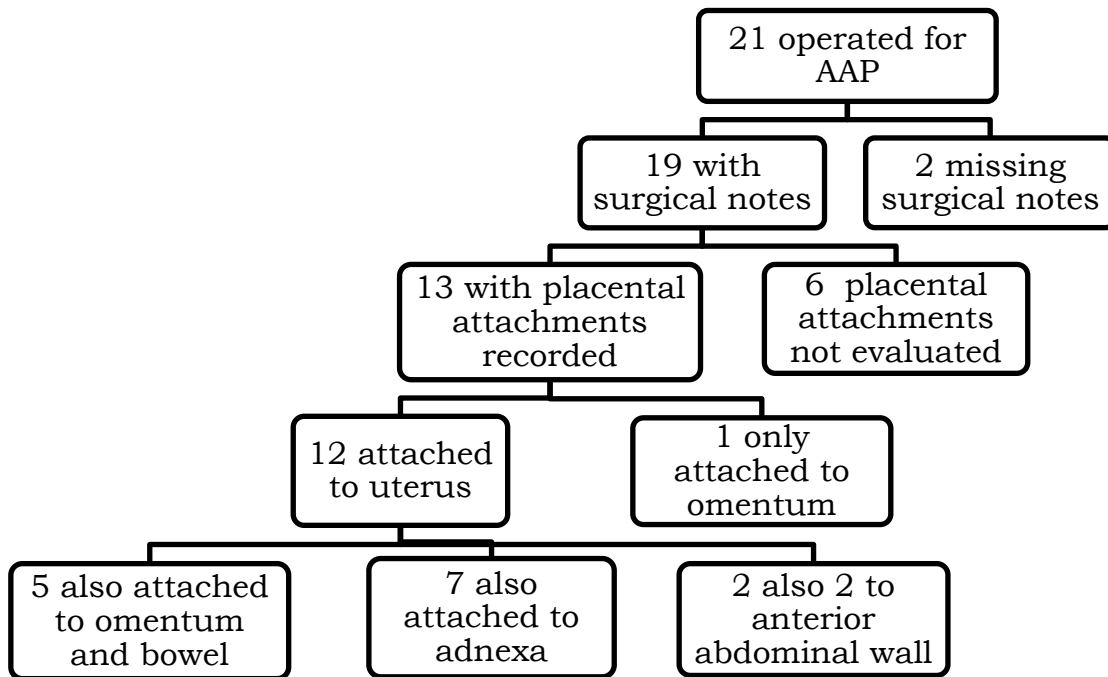
Surgical notes were not found in 2 (9.5% of 21) patients thus abdominal entry and abdominal findings could only be described in 19 (90.5% of 21) patients. A high left paramedian incision was made in 8 (42.1% of 19) patients. A sub-umbilical midline incision was made in 6 (31.6% of 19) patients; and required extension above umbilicus in some patients. An upper midline incision was used in 4 (21.1% of 19) patients. The one (5.3% of 19) patient operated initially as a caesarean section at the district hospital had a lower transverse incision, converted to an inverted 'T'.

Haemoperitoneum was found in 3 (15.8% of 19) patients. Thirteen (68.4% of 19) fetuses were in an intact gestational sac and 6 (31.6% of 19) were free in the abdomen. Placental site bleeding was present in 7 (36.8% of 19) patients; this included the 3 with haemoperitoneum. The seven patients with placental bleeding were all noted in patients in whom the foetus was in a gestational sac. None (0% of 6) patients in which the foetus was freely-lying had placental bleeding.

5.6.3. Placental attachments

To avoid provoking uncontrollable haemorrhage, placental attachments to pelvi-abdominal organs were not extensively evaluated. Thus for 6 (31.6% of 19) patients for whom operation notes were available; there were no details of where the placenta was attached, see Figure three below. The placenta was attached to the uterus in 12 (92.3% of 13) patients whose placental attachments were documented. In the twelve patients where the placenta was attached to the uterus, it was also noted to be attached to adnexa in 7 (53.8% of 13) patients, omentum and bowel in 5 (38.5% of 13), and the anterior abdominal wall 2 (15.4% of 13) patients. It was noted to be solely attached to omentum in one (7.7% of 13) and not explored further.

Figure Three: placental attachments



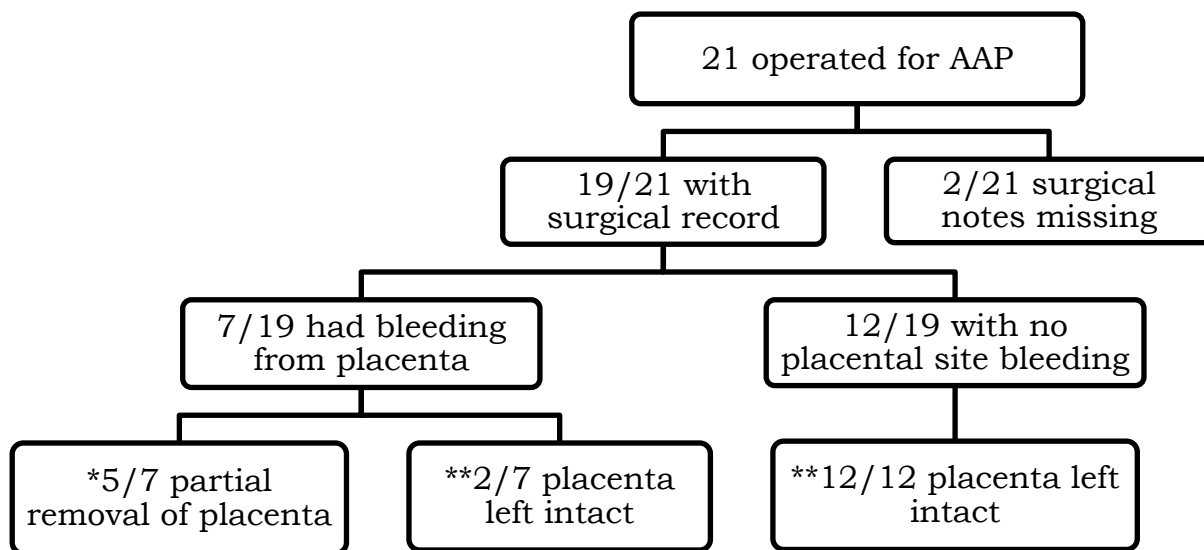
5.6.4. Surgical management

A total of 21 patients were operated for AAP. Two (9.5% of 21) began as a CS, 18 (85.7% of 21) were planned procedures for AAP and one (4.8% of 21) patients was an emergency procedure for known AAP with hypovolaemic shock. All patients were operated under general anaesthesia except the one initially operated as a supposed caesarean section at the district hospital. She was operated under spinal anaesthesia and only converted to general anaesthesia on diagnosis of AAP intra-operatively.

Details of placental management are presented for the 19 patients in Figure four below. Of those with surgical notes available, 14 (73.7% of 19) patients had the placenta left intact. This included 12 (63.2% of 19) patients, where there was no

placental site bleeding and two (10.5% of 19), where there was already some placental site bleeding, but haemostatic sutures controlled the bleeding. For five (26.3% of 19) patients; who already had placental site bleeding, partial removal of placenta was performed. In one of these a partial omentectomy was also required to stop bleeding. No patient required adnexectomy, bowel resection or hysterectomy at initial surgery.

Figure Four: Surgical management of placenta



**Five (26.3% of 19) had partial resection of placenta.*

***Fourteen (73.7% of 19) had placenta left intact.*

5.6.5. Intra-operative complications

Of the 21 patients operated for AAP, 2 had surgical operation notes completely missing and some files also lacked some significant information. There was no record of any visceral injury sustained during surgery for all (100% of 19) patients operated for AAP who had theatre operation notes available. There was however poor recording of estimated blood loss at surgery; a record was only found in ten (47.6% of 21) patients and was missing from all theatre records in

11 (52.4% of 21). At initial surgery, severe PPH (>1000mls) was recorded in three (30% of 10) patients and massive PPH (>2.5 litres) in one (10% of 10) patient. These were all in the patients who had placental removal.

Three (15.8% of 19) patients had difficult surgery with significant blood loss. The first was the patient known with AAP down referred for expectant management and re-admitted as an emergency with haemorrhagic shock that had approximately 3000ml of haemoperitoneum. She required partial omentectomy and almost complete removal of the placenta to achieve haemostasis. The second was the patient diagnosed at CS at the district hospital. She had estimated blood loss at the supposed caesarean section of 2000ml. After failing to achieve haemostasis she was referred to RFH with ongoing transfusion along the way. At relook laparotomy was found to have a haemoperitoneum of 3000mls and required a hysterectomy. She received in total, 14 units of packed RBC, 10 units of FFP/ fresh dried plasma (FDP) and 3 pooled platelets. She required a second relook laparotomy, developed severe coagulopathy and died. The third was a patient in whom the placenta was accidentally cut through at abdominal entry.

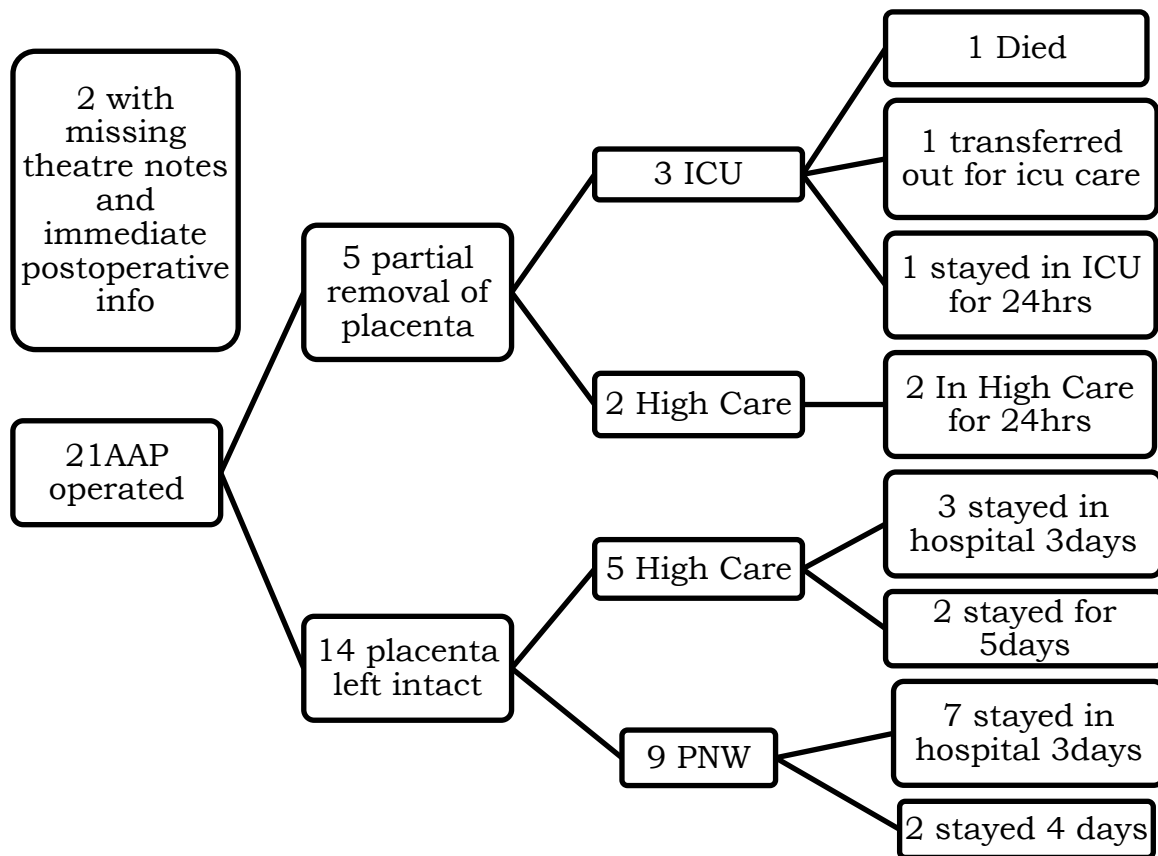
The duration of surgery for all AAP was 56.4 minutes (range 20-123). The 14 (73.7% of 19) patients in which placenta was left intact, had relatively shorter duration of surgery; mean of 45 minutes (range 20-110). The five (26.3% of 19) who had partial removal of placenta had a mean duration of surgery of 95.6 (range 55-123) minutes.

A relook laparotomy was required in two (10.5% of 19) patients. The first was the patient who died (described in previous paragraph) and the second was for a patient who initially had had the placenta left in-situ. At re-laparotomy, suturing at the edges, reflecting the edges inside, followed by deep purse string suture, was enough to achieve haemostasis.

5.7. Postoperative course:

The postoperative courses of the patients operated for AAP are described in Figure five below. Two (9.5% of 21) patients had information on the immediate postoperative course missing; however, according to the maternal mortality register, neither died nor suffered severe morbidity. The postoperative maternal outcomes of 19 (90.5% of 21) are thus described. Two patients needed relook laparotomy immediately post initial surgery as described in the previous section.

Figure Five: Postoperative course



Three (15.8% of 19) patients required Intensive Care Unit (ICU); this included the patient who died. Seven (36.8% of 19) patients were managed in a High care, for intensified observation, but did not need intubation and ventilation

postoperatively. They were all transferred to the general postnatal ward the following day. Nine (47.4% of 19) were admitted straight to the general postnatal ward immediately after surgery. All patients were given prophylactic antibiotics; and no patient developed clinical signs of sepsis before discharge. Sixteen (84.2% of 19) patients had an uneventful postoperative course. The mean length of hospital stay was 3.4 (range 3-5) days.

5.8. Maternal morbidity and mortality

Immediate post-operative records were unknown for 2 (9.5% of 21) patients, but as mentioned previously, neither died. There was one maternal death giving a CFR in this AAP series of 47.6 per 1000. Seven (36.8% of 19) patients were classified as a near miss according to Say (2009) for World Health Organization (WHO) criteria. This includes patients who had >4 units blood, required intubation and ventilation, required a hysterectomy and required a relook laparotomy for haemorrhage.

One of the patients with AAP was seen on day seventeen for superficial wound sepsis and discharged on oral antibiotics. However, scheduled follow-up was not routine practice so long-term outcomes on the study group could not be reported on.

5.8.1. Maternal outcomes and placental site bleeding surgical management

Table 5 describes short term maternal outcomes in patients with and without placental removal. Although numbers are small, those with placental bleeding on abdominal entry and for whom partial removal of placenta was required, tended to have more haemorrhage, near misses and interventions.

Table 5: Maternal outcomes and interventions in women with and without placental removal

Parameters compared	14 patients with placenta left intact		5 patients with partial removal of placenta	
	Number of patients (mean)	Percentage (range)	Number of patients	Percentage
Transfused ≥ 4 units packed cells	2	14.2%	5	100%
Intubation/ventilation and ICU admission	0	0	3	60%
High Care admission	5	35.7%	2	40%
Postnatal ward straight from theatre	9	64.3%	0	0
Relook laparotomy	1	7.1%	1	20%
Length of hospital stay (days)	3.4	3-5	3.67**	3-5
Sepsis*	1	7.1%	0	0
Death	0	0	1	20%

*superficial wound sepsis, on day 17 post laparotomy managed with oral antibiotics, managed as outpatient.

**Length of hospital stay only for 3 patients, 1 of the 5 patients died within 5 days, 1 was transferred to another hospital for ICU care, duration of which is unknown.

5.8.2. Maternal outcomes and location of foetus in gestational sac or free in abdomen

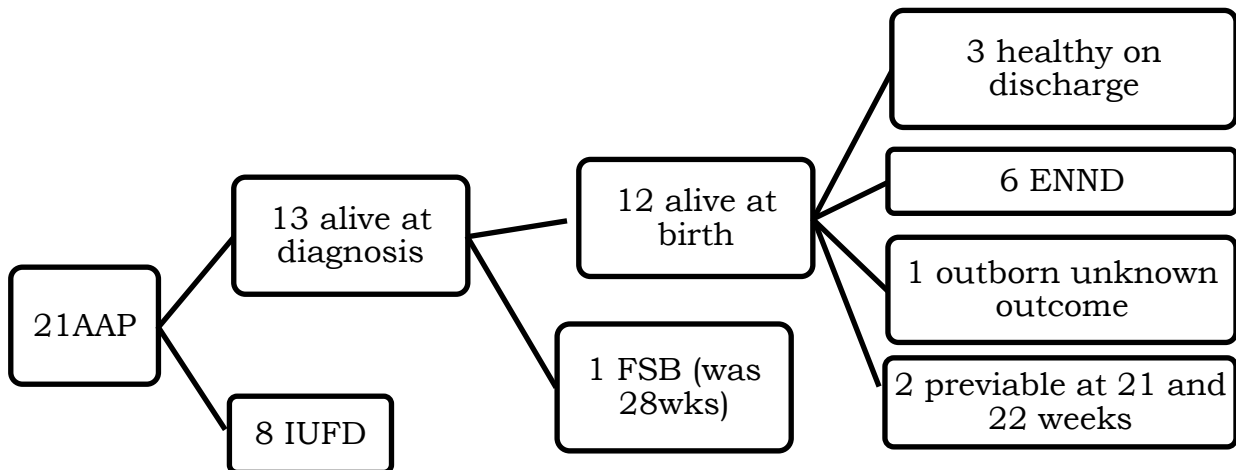
Numbers are too small to make conclusions, but it is interesting to observe the relation of maternal outcomes to how the foetus was lying in the abdominal cavity. It appeared to be better when the foetus was found freely lying among abdominal organs than in a gestational sac; six (28.6% of 19) of the foetuses were found free in the abdominal cavity, 13 (61.9% of 19) foetuses were enclosed

in gestational sac, and in two (9.5% of 21) fetuses location was not recorded. All the seven (36.8% of 19) noted to be bleeding from the placental site had the fetus enclosed in a gestational sac. They suffered more morbidity and one mortality. The duration of surgery in this group was 72.9 (35-123) minutes. The six that were lying freely in the abdomen had no placental site bleeding at all. Their mean duration of surgery was 26.6 (20-40) minutes. Only two (33.3% of 6) patients who had a free fetus were found to be anaemic pre-op and were transfused 1 unit each to optimize them.

5.9. Perinatal outcomes

Perinatal outcomes of the 21 AAP babies are annotated in figure six below. There were 9 (42.8% of 21) SBs, 2 (9.5% of 21) pre-viable, 6 (28.6% of 21) ENNDs, 3 (14.3% of 21) discharged alive and one (4.8% of 21) delivered alive at the district hospital with unknown perinatal survival outcome. The majority, 15 (78.9% of 19) neonates, with recorded gender were female.

Figure Six: Perinatal outcomes



There were 15 known perinatal losses, giving a pregnancy loss in women with AAP of 71.4%. The one fresh SB was in the patient with emergency surgery done for intra-abdominal bleeding. The two (9.5% of 21) pre-viable babies (21 and 22 weeks), died immediately after birth.

Of the 9 babies born alive, 8 had received antenatal steroids. Six (28.6% of 21) neonates suffered ENND due to lung hypoplasia and acute respiratory distress syndrome. Three (14.3% of 21) infants were discharged alive. They had all been given 48-hour course of antenatal corticosteroids after diagnosis at 29-31 weeks. Only 2 had weights documented at birth and discharge. One was delivered at 29 weeks, weighed 1360 grams (g) at delivery, discharged at the same weight after 11 days in the neonatal ICU. The second one was born at 31 weeks, birth-weight of 1730g and discharged at 1760g after 9 days in hospital. Overall, neonatal survival in patients with AAP was therefore 14.3% (3 out of 21).

Birth weight data was only recorded for 12 babies and ranged from 1300 to 2600g. Three (14.3% of 21) infants had recorded but not fully described foetal abnormalities; 2 were ENNDs and one was discharged alive with a weight of 1360g.

5.9.1 Perinatal outcomes and location of foetus in gestational sac or free in abdomen

Numbers are too small to conclude associations; however it is interesting to describe this outcome. At surgery, six (28.6% of 21) foetuses were found free in the abdominal cavity and 13 (61.9% of 21) enclosed in a gestational with the data missing in two (9.5% of 21). Of those found in a gestational sac, six (46.2% of 13) were alive at birth, of which one baby (7.6% of 13) survived. In contrast, five (83.3% of 6) foetuses found free in the abdomen were delivered alive, and neonatal survival rate was two (33.3% of 6).

CHAPTER 6: DISCUSSION

6.1. Summary of main findings

This study describes 21 patients with AAP managed over 7 years in a resource constrained setting. The small numbers reflect the rarity of the condition and most other case series have numbers of similar magnitude. The findings may be applicable to similarly resourced settings but may fall short of investigative and management procedures available in well-resourced settings. In such settings, other investigations such as MRI may enable better delineation of placental attachments, including the vessels supplying it. Such tests may then provide more information to make decisions on the possibility to remove the placenta without causing catastrophic haemorrhage. Also, the availability of a multidisciplinary team for case discussion, and involvement of haematologists, general and vascular surgeons including interventional radiology techniques may enable devascularisation of the placenta before its removal.

This case series confirm that AAP is a serious condition with one of the 21 patients dying and seven suffering severe morbidity. The CFR of 47.6 per 1000 compares well with other studies. Most of the reviewed studies did not measure the near miss rate which has only become a maternal health indicator in the last decade (Say 2009). However, our near miss rate of 36.8% patients is lower than the morbidity described by most studies in older and relatively newer literature, including experiences from the developing and developed countries (Dixon, 1960; Yahia, 1956; White, 1989; Golan, 1985 and others). Worley (2008), at Parkland hospital, in the Texas study, USA, reported morbidity that could be classified as near misses in at least nine (90%) of the 10 patients. In their study, pre-operative diagnosis of AAP was only made in 5 patients, there was a high hysterectomy rate and severe sepsis occurred in 2 patients with placenta left in situ.

The reason for the lower near-miss rate in our series is likely to be multi-factorial. Firstly, 90.4% of patients were diagnosed pre-operatively and 85.7% were planned procedures, so that a detailed preoperative plan for surgery could be made. Secondly, one skilled senior surgeon performed most of the surgery. Thirdly, routine use of antibiotic prophylaxis may have contributed to low rates of sepsis. The woman discovered to have AAP at a supposed caesarean section had the worst outcome. This may have been due to the absence of pre-operative planning, compounded by the lack of appropriate surgical skill at the initial surgery, performed by a medical officer at a district hospital with no on site specialist support and limited blood products.

Although numbers were small; the patients for whom there was haemoperitoneum and bleeding from the placental site noted at abdominal entry, that necessitated more surgical intervention, appeared to have higher rates of complications; need for blood transfusion and need for intensive care. Those with no observable bleeding and in whom the placenta was left undisturbed, had a trend for better outcome. In this series placenta removal was only attempted in patients who already had haemorrhage as advocated by Cartwright, 1986; Delke, 1982; Hallatt, 1985 and all their co-workers. The only patients in whom an injudicious attempt at placental removal provoked massive bleeding were firstly the district hospital patient in whom AAP had been unsuspected; and secondly the patient in whom the placenta was inadvertently cut through on abdominal entry.

This finding is partly in agreement with White, 1989 and Clark, 1975 who concluded less mortality in patients where the placenta could be left intact. However, leaving placental tissue in our series was not associated with severe sepsis, contrary to what these two researchers concluded from their case series. Only one, 4.8% patients who had placenta left intact; presented with superficial wound sepsis on day 17. However, long term outcomes may have been

underestimated in this study because patient follow up tended to be only until the date of discharge from hospital.

6.2. Limitations of the study:

The sample size was too small to perform comparative analysis or make definite recommendations. Also, comparative data on the general population was not available in order to identify risk factors for AAP. An estimation of the incidence of AAP at RFH was performed but since it is a Provincial tertiary hospital with a large catchment area the true incidence of AAP should include in the denominator all deliveries at home and in facilities referring in to RFH, and thus overall AAP incidence would be lower. It is assumed that all patients with AAP were transferred for management from Ehlanzeni district to RFH; however, it is possible that some AAPs might have also been managed at district and/or secondary hospitals; with unknown outcomes and could have influenced the numerator.

Surgical notes were missing in 9.5% patients; for whom details of placental attachments and management were thus not noted. One patient was immediately transferred out for ICU admission to another facility in the province, thus the immediate postoperative details are unknown. Birth weights were poorly recorded. Notes for the neonates were also incomplete.

Only short term maternal and neonatal outcomes were measured, thus maternal septic morbidity may have been underestimated. Further discussion of the Results now follows, given the limits in interpretation.

6.3. Incidence:

Twenty-one patients with AAP were analysed in this review. They were identified among 31, 717 deliveries at RFH. The incidence of 1 in 1510 deliveries (or 66.2 per 100, 000 deliveries), with a mean of 3 per year, is high when compared to reports in the literature and similarly poorly resourced settings, apart from one review in older literature by Dixon (1960) which reported a much higher incidence of 107.5 per 100, 000 deliveries. Yahia (1956), from a similar period, however, reported a much lower incidence of 11.7 per 100,000 deliveries. It is however difficult to compare incidence, even with local reports, because of no universal agreement of the definition of “advanced” abdominal pregnancy and differences in the nature of the denominators used with respect to them being facility or population figures. The incidence in this series is much higher than the incidence reported by Rahman (1982) of 9.8 AAP per 100, 000 deliveries and Worley (2008) of 4 per 100, 000 deliveries.

6.4. Socio-demographic and clinical characteristics:

Due to the small numbers and lack of comparison group, the data on age, parity and other demographic factors cannot be used to show associations with or risk factors for AAP. The results of mean age 30 yrs, median parity 1 and prior CS rate of 9.5% is similar to other case series.

However, the high prevalence of 78.9% HIV infection in patients with AAP was much higher than the HIV prevalence among antenatal women for Ehlanzeni district of 35.8% to 39.2% over the same time period (The 2015 National Antenatal Sentinel HIV & Syphilis Survey, South Africa National DOH). The significance of this finding is not clear. Leyva (2011), also from South Africa, in their case report of 3 cases raised questions about the specific management of the placenta in HIV positive patients with AAP; its influence on HIV transmission to the infant with untreated maternal HIV and the possibility of compounding

the already reported high rates of sepsis associated with leaving the placenta in situ. The risk of HIV vertical transmission in AAP, especially noting the associated higher incidence of HIV in this group of patients, is an area of further research. The aim in all patients was to leave the placenta undisturbed irrespective of HIV status. We gave all patients antibiotic prophylaxis, with cefazolin which was continued after surgery. The 6 weeks PCR for one of the babies was negative.

6.5. Diagnosis

The presenting symptoms and signs of AAP in this study are similar to those found in literature. They ranged from being asymptomatic to having had multiple presentations prior to diagnosis. In this series, 84.2% patients presented 2 to 5 times with symptoms before the diagnoses were made. All (100%) patients presented with abdominal pain and 63.2% reported absent FMs and 42.1% were found to have an IUFD; this is similar to the series by Rahman (1982). These findings suggest a suspicion of AAP must be considered for all women with recurrent admissions after 20 weeks for abdominal pain without labour, especially if an IUFD is discovered.

Investigations

All the 21 patients with AAP in our series had at least one ultrasound scan. No other modalities of investigations were employed. USS was done by medical personnel with different experiences, ranging from medical intern to gynaecologist. All those who were strongly suspected to be AAP were then confirmed to be such at RFH, prior to surgery. Overall, 90.5% were diagnosed pre-operatively by USS. A failure to induce contractions with an IUFD was also a very reliable predictor for AAP. We thus agree with Ombelet, (1988) and Suren (1998) that with a high index of suspicion, USS is the best diagnostic tool. However, our study agrees with other researchers that many cases (at least 50%)

are missed on initial USS, and the diagnosis is often only confirmed on repeat USS when more suspicion has been generated. USS diagnostic accuracy, with MRI as an adjunct for diagnosis and to delineate placental attachments, was 60% diagnostic in the series of Worley (2008).

The USS technique described by Edmonds (2012) should be followed; a transvaginal scan is performed to establish continuity between cervical canal, uterine cavity and gestational sac. Failure to induce labour with other methods including prostaglandins was important in the diagnosis of 33.3% of our patients. At RFH, a repeat USS after failure to induce labour is now recommended solely to establish if the pregnancy is intrauterine.

6.6. Perioperative evaluation and planning:

Surgery was always necessary for our patients with AAP and no other treatment modality was used. Elective surgery was planned for 90.5% patients. One of the controversies in AAP management is whether and for how long surgery can be delayed when the fetus is alive and the mother haemodynamically stable. In our study, surgery was delayed successfully for up to 48 hours to await experienced staff, to complete a 48-hour course of antenatal steroids, and to transfuse blood. For two patients, a plan was made to delay surgery for 2 weeks or more. This was successful for only one patient, albeit with poor outcome for the infant who was dysmorphic and died immediately post-delivery due to pulmonary hypoplasia. The other patient had to be operated as an emergency with massive intra-abdominal bleeding about 2 days after being down referred and a FSB was delivered. Although our numbers are small, they do suggest that whilst it appears safe to defer surgery for AAP with live baby and stable mother for 48 hours, waiting longer should be done with caution and only in a tertiary facility.

6.7. Surgical Management and associated maternal morbidity/ mortality:

In contrast to Worley (2008), the RFH surgical approach to AAP is to enter the abdomen and deliver the foetus with as little trauma to the placenta as possible in the hope to not provoke any potential haemorrhage. The intention at RFH was to leave the placenta undisturbed in all patients, unless placental site bleeding had already occurred. Clark (1975) and other researchers asserted that removal of the placenta was associated with the lowest morbidity but highest mortality rate. Cartwright, 1986; Delke, 1982; Hallatt, 1985 and all their co-workers advocate for placenta removal especially if there is already haemorrhage. Conversely leaving the placenta is associated with more postoperative sepsis.

With this ongoing debate, RFH follows suggestion by Edmonds (2012) and Cunningham (2014) for managing AAP. At surgery, delivery of foetus was done with utmost care to prevent disruption of the placental bed, and the placenta left intact if not bleeding after inspection. The placenta was partially removed only when there was already bleeding. Circumferential resection of the placenta, a running suture of the edges followed by purse string suturing with edges reflected into the centre was mostly used successfully to tamponade the bleeding. The senior specialist at RFH has developed the skill to manage these patients and operated on 94.7% patients. This emphasises the need for a high level of skill to be available to operate on AAP and to refer or delay surgery up to 48 hours if the mother is haemodynamically stable.

Although small numbers, our study concur that it was safe to leave the placenta undisturbed if there is no bleeding. It also found that the greatest morbidity occurred in those who had placental site bleeding with and/or without haemoperitoneum and required partial placental removal. This approach did not seem to be associated with sepsis for those in whom the placenta was left but inadequate long term follow-up may limit the veracity of this finding.

6.8. Perinatal Outcomes

Poor perinatal outcomes for AAP are reported in this study similar to reports in literature. Overall, neonatal survival rate was 14.3% with a pregnancy loss in patients with AAP of 71.4% which is similar to the loss of 72% reported by Nkusu (2008). Perinatal loss was 83% in Harare (White, 1989). Perinatal care which is obviously less ideal in resource constrained settings such as ours in comparison with high resource settings, compounds the risk for these already at-risk neonates. Stevens (1993) reviewed literature from 1809 and noted that the survival rate of infants born alive at 30 or more weeks was 63%. Rahman (1982) reported better perinatal survival of 50% in comparison to ours. All three infants that were discharged alive had been given 48-hour course of antenatal corticosteroids.

The absence of the normal intrauterine environment, suited for normal fetal growth, is responsible for a higher rate of gross fetal abnormalities and deformities. We report 15.0% of newborns had gross fetal abnormalities; similar to the 20% rate of malformations and deformations in the report by Stevens (1993). The types of abnormalities are not fully evaluated in our series. In their summary already described above, Nkusu (2008) showed that pressure deformities of face, skull and limbs were common among the 18% of survivors. Multiple pressure deformities are also reported from Harare.

We have no explanation of why maternal and perinatal outcomes in AAP appeared to be worse when foetuses were found enclosed in a gestational sac, in comparison to when free in abdomen. Stevens (1993) found no statistically significant difference between the two groups in perinatal outcomes except higher rates of pulmonary hypoplasia in those freely lying. It may be related to the underlying nature of the vascular connections and this preliminary finding requires further exploration in the literature. The reviewed literature makes no distinction for maternal outcomes related to this finding.

These findings on poor perinatal outcome in this study and in the literature should inform counselling of mothers with a diagnosis of AAP. Management is aimed chiefly at saving the mother's life and the possibility of neonatal survival cannot be guaranteed.

6.9. Recommendations for future practice:

1. An upgrade in antenatal services with the provision of early USS for all pregnant patients would assist earlier diagnosis of extra-uterine pregnancy. Training of antenatal providers on basic USS should be priority.
2. AAP should be strongly suspected after failed IOL for IUFD, and in women with recurrent admissions for abdominal pain.
3. Patients with suspected AAP should be promptly referred for higher care, and preferably should be managed at tertiary hospitals by the most skilled specialist.
4. After diagnosis of AAP, strict criteria need to be used to assess eligibility to delay surgery, and only with vigilant in-patient care.
5. Pre-operatively, AAPs need to be discussed with all disciplines that are likely to be involved in the management of these patients.
6. Extensive surgical training and refresher courses should be facilitated, for medical practitioners working in poor resource settings including district hospitals. Such training should include skills to recognize AAP and not disrupt the placental attachment when not bleeding, but also to manage massive bleeding when the placenta has already detached. Suspected difficult cases at district hospitals should be discussed with specialists at RFH before they are taken for operation. If difficulty is encountered, the doctors at district should discuss the cases intra-operatively.
7. It is important to organise follow up of these patients particularly to check for maternal infectious morbidity and long-term neonatal outcome

CHAPTER 7: CONCLUSION

This study shows that planned management of AAP in a resource constrained setting with tailored approach and management, can be performed without compromising maternal outcomes. However poor outcomes occurred when pre-operative diagnosis was not made, and AAP was discovered during emergency CS, emphasising the importance of antenatal diagnosis. USS and a high index of suspicion remains the best diagnostic tool. From this study it appears safe to leave the placenta undisturbed unless it can be safely removed, or the patient is already bleeding from the placental site. The descriptive methodology and small sample size did not enable any comparative analyses of risk factors or management approach. Long term maternal and foetal outcomes are area of further research. There were very low neonatal survival rates.

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Appendix A: HREC UCT



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room 253-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 August 2018

HREC REF: 482/2018

Prof S Fawcus
Department of Obstetrics & Gynaecology
H-Floor, OMB

Dear Prof Fawcus

PROJECT TITLE: ADVANCED ABDOMINAL PREGNANCY: DIAGNOSIS, EVALUATION AND SURGICAL MANAGEMENT IN A RESOURCE CONSTRAINED SETTING (master's candidate - Dr R Elijah)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study, subject to: - The HREC note the permission from Rob Ferreira Hospital; but not no local REC approval. Please confirm this has occurred.

Approval is granted for one year until the 30 August 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Regis Elijah will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely


PROFESSOR M. BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Appendix B: Mpumalanga LEC Approval



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Prof. Susan Fawcus
Groove Shuur Hospital
Cape Town
7925

Dear Prof. Susan Fawcus

APPLICATION FOR RESEARCH & ETHICS APPROVAL: ADVANCED ABDOMINAL PREGNANCY: DIAGNOSIS, EVALUATION AND SURGICAL MANAGEMENT IN A RESOURCE CONSTRAINED SETTING

The provincial health research committee has approved your research proposal in the latest format you sent.

- Approval Ref Number: **MP_201807_007**
- Period: **06/11/2018 to 31/12/2018**
- Facilities: Rob Ferreira Hospital

Kindly ensure that the study is conducted with minimal disruption and impact on our staff, and also ensure that you provide us with the soft or hard copy of the report once your research project has been completed.

Kind regards


MS. T.Z MADONSELA
MPUMALANGA PHRC


DATE



Appendix D: Declaration- Word count form

UNIVERSITY OF CAPE TOWN FACULTY OF HEALTH SCIENCES FORM D18 - DECLARATION/WORD COUNT FORM -- MASTER'S DEGREE CANDIDATES					
Title:	Dr	Student No:	ELJREG001		
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Dissertation Title:	ADVANCED ABDOMINAL PREGNANCY: diagnosis, evaluation and surgical management in a resource constrained setting.				
Supervisor	Prof Sue Fawcus	Word count	11, 147	No. of pages	45

IMPORTANT NOTES:

- 1.1 Candidates for graduation in June and December may expect to receive notification of the outcome of the examination of the dissertation not later than 1st week in June and last week in November, respectively, provided the dissertation was submitted by the due date. Where a dissertation has been submitted well in advance of the due date, earlier notification will be given, if possible. However, the University does not undertake to reach a decision by any specific date.
- 1.2 Candidates who are required to revise and re-submit for re-examination are required to register during the revision phase. Fees will be calculated according to the date of the notification of the "revise and re-submit" result and the date of re-submission. [Faculty will advise Fees by sending copy of R&R result to Fees.]
- 1.3 Candidates are asked to note that the University will not permit degree/diploma qualifiers to graduate if they have any outstanding fees, fines, interest or dues. **The final date for payment of outstanding amounts is 30 April in the case of qualifiers for June graduation and 31 October in the case of qualifiers for December graduation.**
- 1.4 Please note that should your examination process run into the following year, you will have to re-register in order to be considered for graduation.

2 DECLARATIONS:

- 2.1 I am presenting this dissertation in PARTIAL fulfilment of the requirements for my degree.
- 2.2 I know the meaning of plagiarism and declare that all of the work in the dissertation, save for that which is properly acknowledged, is my own.
- 2.3 I hereby grant the University of Cape Town free licence to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever of the above dissertation.

Signature	Signed by candidate	Date:	13/05/2019
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3 FUNDING AND FEES:

Candidates submitting have a choice in regard to fees and funding options:

- 3.1 To claim a fee rebate* and discontinue funding through the PGFO, if applicable (the student remains registered until graduation or the start of the next academic year (see University Rule G5.2).
*(Only applicable in second or subsequent year in which the dissertation is being completed - Fee Rule 8)
- 3.2 To remain registered and engaged in the department while **writing up a paper for publication**, with full student rights and full access to facilities, full liability for fees for the year and continued eligibility for funding already awarded for that academic year. Access will extend only until such time as you graduate. Should you need access beyond this, you will need to arrange for 3rd party access within your department.

Please indicate your preference

I wish to claim the rebate and discontinue funding (if applicable) and physical and library access**	Yes
I wish to continue fee liability, funding eligibility (if applicable) and access to all facilities	No

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- a) the implications of the fee rebate on their access to facilities and eligibility for funding, and
- b) That if they were to stay on in the department and receive payment through the payroll, such payment is taxable.

<i>Signature</i>	Signed by candidate	<i>Date:</i>	MAY 13, 2019
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FOR COMPLETION BY FACULTY OFFICE

I acknowledge receipt of the uploaded copy (on PeopleSoft) of the Master’s dissertation of the above candidate submitted for examination:

<i>Signature</i>		<i>Date:</i>	
<i>Abstract submitted</i>	Yes		No

- cc **Fees**
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