1 A: TITLE PAGE
2
3 1. TITLE:
4 Sepsis: Primary indication for peripartum hysterectomies in a South African setting
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Sepsis is the most common indication for peripartum hysterectomies in this study and the incidence may be underestimated if the time period included is short.

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The study was approved by the University of Stellenbosch, Health Sciences ethics committee (S13/08/155).
B: ABSTRACT

BACKGROUND:
Peripartum hysterectomies are lifesaving procedures but definitions vary. Indications are variable and dependant on resources and geographical factors.

OBJECTIVES:
This study evaluates the incidence, aetiology and complications associated with peripartum hysterectomies in a tertiary hospital in South Africa.

METHODS:
A retrospective audit at an academic referral center over a five year period from February 2009 to March 2014 was performed. Procedures from a gestational age of 24 weeks until six weeks postpartum were included.

RESULTS:
One hundred and sixty cases met inclusion criteria. Nine case records were unavailable. The incidence was 2,77 per 1000 deliveries. Main indications were sepsis (60, 39,7%), uterine atony (24, 15,9%), morbidly adherent placenta (21, 13,9%), tears (14, 9,2%), uterine rupture (8, 5%), placenta praevia (7, 4,6%) and unclassified bleeding (6, 4%). There were 6 maternal deaths. Five related to sepsis and one to hypovolaemic shock. One hundred and thirty eight (91,4%) women required high or intensive care admission.

CONCLUSION:
Sepsis is an important aetiology for peripartum hysterectomies, particularly in Southern Africa. The high rate of sepsis may be due to HIV infection, low socio-economic standards, late diagnosis, limited access to health care, sterility issues and differences in the definition and inclusion criteria used for a peripartum hysterectomy.
C. MAIN TEXT:

INTRODUCTION

A peripartum hysterectomy is a lifesaving procedure performed usually as an emergency that can be associated with significant morbidity and mortality(1). Despite many publications, the definition of a peripartum hysterectomy remains vague. Definitions include a hysterectomy performed within 24 hours of delivery(2-5), a hysterectomy performed within the same hospitalization(6-10), a hysterectomy performed within 72 hours of delivery(11), a hysterectomy performed within one month of delivery(12,13) to a hysterectomy performed within six weeks of delivery(14). Some even limit the definition to a hysterectomy performed for only uncontrolled haemorrhage (4,15-22) and exclude cases of infection(12). The varying definitions make it difficult to compare incidences and aetiology. If a short time period after delivery is used complications from sepsis and delayed haemorrhage may be underestimated.

Peripartum hysterectomies complicate about 1 in 1000 pregnancies (23). The incidence is lower in higher resource settings. In a large review from the United States the incidence was 0.77 per 1000 deliveries (10) while African countries have reported higher incidences ranging from 4.34 to 9.5 per 1000 deliveries(9,14,17,19). Lack of antenatal and peripartum care due to limited resources, a high burden of HIV infection and a delay in recognizing complications may be reasons for the increased incidences.

In high resource settings complications of placentation are the most common indication for peripartum hysterectomies (5-8,11,12,22,24,25). In middle income countries the aetiology is variable with studies from Turkey, India and Thailand showing similar indications to high resource settings but with higher rates of uterine rupture (4,15,16,21,26-28). Sepsis has been reported as an indication in
low resource settings. In Africa the most common aetiologies include uterine rupture, atonic uteri and sepsis (14,19,29-31).

Three studies performed in tertiary care settings in South Africa have shown particularly high rates of sepsis. A study performed in Mthatha showed uterine atony, puerperal sepsis and secondary postpartum haemorrhage made up 57% of the indications. The morbidly adherent placenta was the least common indication (9). In a review of cases from Durban, uterine rupture and sepsis made up 56% of the indications (29) and a study from Pretoria reported that puerperal sepsis was the second most common indication after ruptured uteri and accounted for 33% of peripartum hysterectomies (31).

Observational data in our department at Tygerberg Hospital, a tertiary referral center in Cape Town, suggested that sepsis was a common indication. This study was therefore designed to systematically evaluate the incidence, aetiology and complications associated with peripartum hysterectomies in the unit.

MATERIALS AND METHODS

A retrospective audit was performed at Tygerberg Hospital, a state academic referral center over a five year period from February 2009 to March 2014. The study was approved by the local ethics committee (S13/08/155). Cases were identified in theatre record books and individual case records were reviewed. Data was extracted and transferred to an MS Excel spread sheet. The inclusion criteria were all peripartum hysterectomies performed from a gestational age of 24 weeks until six weeks postpartum. Information on patients age, gravidity, parity, gestation, HIV status, CD4 count, ARV usage, medical history, past obstetric history, antenatal care and complications, intrapartum course,
mode of delivery, intrapartum complications, postpartum complications, neonatal outcome, indication
for hysterectomy, type of hysterectomy, surgical complications, estimated blood loss, high care
admissions, blood products required, morbidity, mortality and length of hospital admission was
collected.

STATISTICA version 9 (Stat Soft Inc. 2009) was used to analyse the data. Descriptive statistics were
used to describe the data. Frequencies (counts and percentages), measures of location (mean and
median) and spread (standard deviations and percentiles) were used depending on the distribution of
the data.

RESULTS

In the five year period 172 hysterectomies were identified. Two emergency theatre books were
unobtainable. These contained information on peripartum hysterectomies that may have been
performed from the 25th of October to the 9th of December 2011 and from the 4th of July to the 15th of
August 2013. It is estimated that information on 0 to 12 cases may be missing. Twelve cases were
excluded as the surgery was performed before 24 weeks of gestational age. These cases included three
hysterectomies performed for gestational trophoblastic disease, one performed for an extrauterine
pregnancy and eight performed for miscarriages. Six of the hysterectomies performed for a
miscarriage were for septic retained products and two were for morbidly adherent placentas.

Of the 160 cases that met the inclusion criteria nine individual case records were unavailable. Two of
these women demised and seven were discharged. One hundred and fifty one cases were therefore
included in the analysis. Ninety-six of these women delivered at Tygerberg Hospital and 55 delivered
at a referral center and were transferred due to complications. During this time period there were 34
558 births at Tygerberg hospital, giving an overall rate for peripartum hysterectomies at our institution of 2.77 per 1000 deliveries.

The youngest patient was 14 and the eldest 46 with a mean age of 30 years. The majority was multigravid with a range of 1 to 7 pregnancies. The mean gestation at delivery was 36 weeks with a range from 24 to 42 weeks. One hundred and twenty nine women (85.3%) had one or more antenatal visits with 22 women (14.7%) presenting for the first time in labour. 140 women had singleton pregnancies, 10 patients had twin gestations and one patient had a triplet pregnancy. Of the parous women, 57 (37.7%) had a previous caesarean section with 28 (18.5%) having had one previous caesarean section and 29 (19.2%) having had two previous caesarean sections.

Fifty women (33.3%) were HIV positive. Thirty-three (66%) were on antiretroviral treatment and 18 (40%) had a CD4 count less than 350 when they first presented for antenatal care. During the time period of this study women were initially only started on lifelong antiretroviral treatment if their CD4-count was less than 350. In July 2013 our national guidelines regarding antiretroviral treatment in pregnant women changed. Since then all HIV-positive pregnant women are started on lifelong antiretroviral treatment at their first antenatal visit. Other antenatal complications are documented in table I.

One hundred and two patients attempted a vaginal delivery. Twenty-eight delivered vaginally (17.9%) with one requiring an assisted ventouse delivery. Seventy women (46.4%) went into spontaneous labour and 32 (21.2%) were induced. Indications for induction of labour are documented in table II. Only seven patients had a successful induction that resulted in a normal vertex delivery. The reasons for unsuccessful induction are detailed in table III.
One hundred and twenty three women (81.4%) had a caesarean section. Twenty-seven (22%) were elective and 96 (78.1%) were emergency procedures. The indications for caesarean section are documented in table IV.

The main indication for a peripartum hysterectomy was uterine sepsis (60 cases, 39.7%). Fifty-two (87.6%) of these women were delivered by caesarean section and the indications included fetal distress in 16 cases (30.8%), poor progress in 13 cases (25%) and failed induction in 7 cases (13.5%). Fifteen of the patients (25%) who developed uterine sepsis needing a hysterectomy were induced. Three (20%) received misoprostol, four (26.7%) received prepidil, three (20%) received a balloon catheter, nine (60%) had an artificial rupture of the membranes and eight (53.33%) received oxytocin. Eight patients (53.33%) needed more than one induction method. Thirty-five patients (58.3%) went into spontaneous labour and four patients (6.7%) were not in labour. None of these women were diabetic. Four were morbidly obese. Twenty-one (35%) were HIV-positive and all of these women had either a CD4 count less than 350 (52%) or where not on antiretroviral treatment (48%). The shortest time interval from delivery to hysterectomy for sepsis was 3 days. The majority was performed 7 to 14 days post-delivery with the longest time interval being 41 days.

Uterine atony was the second most common aetiology. Of the 24 (15.9%) peripartum hysterectomies performed for uterine atony six patients (25%) were multigravidas, four (16.66%) had a multiple pregnancy, two (8.33%) had macrosomic fetuses (estimated fetal weight more than 4kg) and eight (33.33%) had a previous caesarean section. Eight (33.33%) had a vertex vaginal delivery and 16 (66.66%) had a caesarean section with eight (33.33%) being elective for previous caesarean section(s), multiple pregnancy, breech presentation and suspected fetal macrosomia. Eight were emergency caesarean sections. Eleven women (45.83%) went into spontaneous labour and five
(20.83%) had an induction of labour. Oxytocin infusion with artificial rupture of the membranes was
the induction method most commonly used. Four of the five patients who had inductions received
more than one induction method.

Morbidly adherent placenta was the third most common indication. Of the 21 cases seven (13.9%) were emergency hysterectomies as spontaneous labour or a significant antepartum haemorrhage occurred before the planned delivery date. Fourteen cases were elective caesarean hysterectomies. Five patients had one previous caesarean section, twelve had two previous caesarean sections and one patient had a previous uterine evacuation of retained products. Three patients had previous normal vertex deliveries.

There were 14 cases (9.2%) of peripartum hysterectomies related to uncontrollable bleeding from tears. Thirteen were tears at emergency caesarean section that extended into the right or left uterine artery. In one of these cases the tear extended into the cervix and in another the tear extended into the cervix and vagina. There was one case of a vaginal tear during a vaginal delivery that extended to the cervix that required a hysterectomy to control the bleeding.

Uterine rupture occurred in eight cases (5.2%). Half of these women had previously delivered by caesarean section. One woman needed a hysterectomy after blunt abdominal trauma. She had a scarred uterus from a previous caesarean section and was 30 weeks pregnant. Three women went into spontaneous labour and four had an induction of labour of which three received misoprostol and one received prepidil and a balloon catheter.
Seven women (4.6%) who had a caesarean section for placenta praevia required a peripartum hysterectomy for placental bed bleeding that was not controllable with conservative methods.

Six women (4%) had a peripartum hysterectomy due to unspecified haemorrhage. In these cases the cause of haemorrhage was not specified in the medical records.

One hundred and one total abdominal hysterectomies were performed and 50 cases were subtotal hysterectomies. In three of the subtotal hysterectomies the cervical stump was removed at a relook laparotomy. The main indications for performing a subtotal hysterectomy were haemodynamic instability and surgical difficulty due to distorted anatomy and/or adhesions.

There were 6 cases of maternal deaths. We were unable to obtain the case records for 2 of these cases but the cause of death on the death certificate was reported to be septic shock. Sepsis was therefore the cause of death in five cases and hypovolemic shock in one case. Of the three cases whose deaths were related to sepsis, where the clinical records were available, only one was HIV positive. She was a 26 year old with a CD4-count of 17, not on antiretroviral treatment and who was known to have chronic hepatitis B infection with liver failure as well as a history of perforated peptic ulcer disease. She had a preterm vaginal delivery, complicated by disseminated intravascular coagulation (DIC) and multiple postpartum haemorrhages requiring repeated laparotomies and transfusions. She developed severe puerperal sepsis and had a septic uterus at the time of hysterectomy. She demised after she had received 70 units of packed red blood cells, 71 units of fresh frozen plasma, 7 units of platelets and 7 units of cryoprecipitate during her hospital admission. The second was a 41 year old multigravida who did not receive any antenatal care. She had a vaginal delivery at term and presented in septic shock 3 days postpartum. She had a cardiac arrest and was successfully resuscitated but sadly demised later that day. The post-mortem examination confirmed active pelvic floor sepsis and tonsillar
herniation due to brain oedema. The third woman was a 33 year old who was induced at 38 weeks for hypertension. She had prolonged rupture of membranes and a caesarean section was performed for fetal distress. One week postpartum she presented in septic shock. At the referring hospital she suffered a cardiac arrest and was successfully resuscitated. A laparotomy was performed and a ruptured sigmoid colon was repaired. A repeat laparotomy was required as she was unresponsive to therapy and a total abdominal hysterectomy was performed. She later demised due to neutropenic septic shock that was unresponsive to treatment. The maternal death related to haemorrhage and hypovolemic shock involved a 19 year old primigravida who was induced for a post-date pregnancy and received misoprostol followed by a balloon catheter. The membranes were then artificially ruptured and oxytocin was given. A caesarean section was performed for poor progress. At caesarean section an atonic uterus was diagnosed. She received ergometrine, prostaglandin F2α and oxytocin. Uterine compression sutures and uterine artery ligation were performed without success. The abdomen and pelvis were then packed with swabs and she was transferred to Tygerberg Hospital. She suffered a cardiac arrest during the surgery and was successfully resuscitated. Unfortunately DIC developed and after two further laparotomies she demised.

Peripartum hysterectomies were associated with significant morbidity. 138 women (91.39%) required either intensive care admission or a high care admission. The majority of women that did not require intensive care or high care admission were elective caesarean hysterectomy cases.

43 women (28.66%) required one or more repeat laparotomies with one patient requiring nine relook procedures. 137 women (90.41%) required blood transfusion. The average (median) amount of packed red blood cells was six units with a range of 1 to 70 units. Ninety-six women (63.58%) were given fresh frozen plasma. The average amount of fresh frozen plasma required was four units with a maximum of 71 units. Fifty-two women (34.44%) required platelets. On average one pool of platelets
was required with a maximum of 7 units being used. Twenty-six patients (17.22%) required cryoprecipitate.

Sixty-nine women (46.31%) required continuous positive airway pressure support and 53 (35.81%) were ventilated with six (4.05%) needing a tracheostomy due to prolonged ventilation. Twenty-two women (14.86%) required inotropic support, 21 (14.19%) developed renal impairment, three (2.03%) developed a deep venous thromboembolism and three (2.03%) developed a cardiomyopathy, two secondary to sepsis and one being diagnosed as a peripartum cardiomyopathy. The mean admission time from peripartum hysterectomy to discharge or death was 10.24 days.

**DISCUSSION**

Sepsis is an important aetiology for a peripartum hysterectomy, particularly in Southern Africa. In this study, sepsis was the most common indication for a peripartum hysterectomy. This is the first study, according to our knowledge, to report this finding. The high rate of sepsis may be due to the high incidence of HIV infection in our community, low socio-economic standards, limited access to health care, late diagnosis of complications, sterility issues in the labour ward and theatre and differences in the definition and inclusion criteria used for peripartum hysterectomies. If the definition for peripartum hysterectomies had been a hysterectomy at delivery or within 24 hours of delivery, or a hysterectomy for uncontrolled haemorrhage we would have had no cases of sepsis and the incidence in this study would have been significantly lower. Defining a peripartum hysterectomy as a hysterectomy performed within 6 weeks of delivery, which is in line with the World Health Organisation’s (WHO) definition of maternal mortality(32), would result in more standard reporting enabling one to compare studies with greater accuracy. Some may argue that even hysterectomies due to miscarriages and gestational trophoblastic disease should be included in the definition as these are also related to pregnancy. Improving access to antiretroviral treatment is important as all the women
who were HIV positive who needed a hysterectomy for the indication of sepsis had a CD4 count less than 350 or where not using antiretroviral treatment. By implementing the WHO treatment program Option B+, which entails starting a single daily dose fixed combination regimen for all HIV-positive women irrespective of the CD4 count and the stage of disease (33), may decrease the rate of sepsis.

Uterine atony, the morbidly adherent placenta, uterine and cervical lacerations and uterine rupture were also identified as important aetiologies for peripartum hysterectomies. The morbidly adherent placental spectrum of disease and uterine rupture is known to occur more commonly with a previous caesarean sections (34) so avoiding unnecessary caesarean sections is important in decreasing the incidence of peripartum hysterectomies. A delay in self and doctor referral and identification of complications has been described as contributing factors that increase morbidity and mortality (35). This is especially important in the case of sepsis and haemorrhage where early identification and treatment may prevent a hysterectomy.

This study did not demonstrate that diabetes is associated with an increased risk for a peripartum hysterectomy, despite our high rate of sepsis and diabetes, which is different to published literature (36). Induction of labour, particularly with prostaglandins, was less of a risk factor than anticipated.

This study highlights the high morbidity and mortality associated with a peripartum hysterectomy. Morbidity and mortality after a peripartum hysterectomy is high and the majority of deaths were associated with sepsis. This is particularly challenging as the majority of septic hysterectomies occur in countries that have limited access to high care and intensive care facilities.
Strengths of this study include the size of the sample and the definition used which includes all hysterectomies performed until 42 days postpartum and does not limit the inclusion to only hysterectomies for uncontrolled bleeding. Disadvantages of the study include that it was a retrospective review.

Studies assessing the aetiology of peripartum hysterectomies should use a definition that extends to 42 days after the delivery to avoid missing cases of sepsis and delayed haemorrhage and hysterectomies performed for all obstetric indications should be included.

Further research should be aimed at assessing why the incidence of sepsis is so high in certain areas particularly in South Africa.

ACKNOWLEDGEMENTS

None

CONFLICT OF INTEREST

None
E. REFERENCES


Table I: Antenatal complications

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (n)</th>
<th>Percentage of patients (%)</th>
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<tr>
<td>Hypertensive related disorders</td>
<td>49</td>
<td>32.45</td>
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<tr>
<td>Hypertension</td>
<td>17</td>
<td>11.64</td>
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<tr>
<td>Pre-eclampsia</td>
<td>19</td>
<td>13.01</td>
</tr>
<tr>
<td>Pre-eclampsia with HELLP syndrome</td>
<td>13</td>
<td>8.9</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>5</td>
<td>3.42</td>
</tr>
<tr>
<td>BMI &gt; 40</td>
<td>14</td>
<td>9.59</td>
</tr>
<tr>
<td>PROM</td>
<td>6</td>
<td>4.11</td>
</tr>
<tr>
<td>APH</td>
<td>15</td>
<td>10.27</td>
</tr>
<tr>
<td>Antenatal sepsis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HIV</td>
<td>50</td>
<td>33.33%</td>
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Table II: Induction of Labour: Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number induced (n 32)</th>
<th>Percentage of total inductions (%)</th>
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<tr>
<td>Hypertensive diseases of pregnancy</td>
<td>17</td>
<td>53.1</td>
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<tr>
<td>Hypertension</td>
<td>3</td>
<td>9.4</td>
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<tr>
<td>Pre-eclampsia</td>
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<td>34.4</td>
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<tr>
<td>Eclampsia</td>
<td>3</td>
<td>9.4</td>
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<tr>
<td>Intra-uterine fetal demise</td>
<td>5</td>
<td>15.6</td>
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<tr>
<td>Postdate pregnancy</td>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>Prolonged rupture of membranes</td>
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<td>9.4</td>
</tr>
<tr>
<td>Previous abruptio placenta</td>
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<td>6.3</td>
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<tr>
<td>Previous intra-uterine fetal demise</td>
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Table III: Reasons for unsuccessful inductions

<table>
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<th>Reason</th>
<th>Number (n 32)</th>
<th>Percentage of total inductions (%)</th>
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<tr>
<td>Fetal distress</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Not progressing to active labour</td>
<td>7</td>
<td>21.9</td>
</tr>
<tr>
<td>Poor progress during labour</td>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>Cephalo-pelvic disproportion</td>
<td>3</td>
<td>9.4</td>
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<tr>
<td>Uterine rupture</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Extra-uterine pregnancy</td>
<td>1</td>
<td>3.1</td>
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## Table IV: Indications for Caesarean section

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>Number (n 123)</th>
<th>Percentage (%)</th>
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<tbody>
<tr>
<td><strong>Emergency Caesarean Section (96)</strong></td>
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<tr>
<td>Fetal distress</td>
<td>31</td>
<td>25.2</td>
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<tr>
<td>Poor progress</td>
<td>17</td>
<td>13.8</td>
</tr>
<tr>
<td>2 previous CS in labour</td>
<td>9</td>
<td>7.3</td>
</tr>
<tr>
<td>Failed induction</td>
<td>7</td>
<td>5.7</td>
</tr>
<tr>
<td>Cephalo-pelvic disproportion</td>
<td>5</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Elective Caesarean Sections (27)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidly adherent placenta</td>
<td>14</td>
<td>11.4</td>
</tr>
<tr>
<td>Placenta praevia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Two or more previous caesarean sections</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>2</td>
<td>1.6</td>
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<tr>
<td>Breech presentation</td>
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<td>1.6</td>
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