

1 **A: TITLE PAGE**

2 **1. TITLE:**

3 Sepsis: Primary indication for peripartum hysterectomies in a South African setting

4

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24 **5. KEY WORDS/PHRASES**

25 Peripartum hysterectomy; Sepsis;

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6. SYNOPSIS (25 words)

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

7. WORD COUNT

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The authors report no conflict of interest

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1 **13. ETHICAL APPROVAL**

2 The study was approved by the University of Stellenbosch, Health Sciences ethics committee

3 (S13/08/155).

4

1 **B: ABSTRACT**

2 **BACKGROUND:**

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

5

6 **OBJECTIVES:**

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

9

10 **METHODS:**

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

14

15 **RESULTS:**

16 One hundred and sixty cases met inclusion criteria. Nine case records were unavailable. The
17 incidence was 2,77 per 1000 deliveries. Main indications were sepsis (60, 39,7%), uterine
18 atony (24, 15,9%), morbidly adherent placenta (21, 13,9%), tears (14, 9,2%), uterine rupture
19 (8, 5%), placenta praevia (7, 4,6%) and unclassified bleeding (6, 4%). There were 6 maternal
20 deaths. Five related to sepsis and one to hypovolaemic shock. One hundred and thirty eight
21 (91,4%) women required high or intensive care admission.

22

23 **CONCLUSION:**

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

5

1 **C. MAIN TEXT:**

2

3 **INTRODUCTION**

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

14

15 Peripartum hysterectomies complicate about 1 in 1000 pregnancies (23). The incidence is lower in
16 higher resource settings. In a large review from the United States the incidence was 0,77 per 1000
17 deliveries (10) while African countries have reported higher incidences ranging from 4,34 to 9,5 per
18 1000 deliveries(9,14,17,19). Lack of antenatal and peripartum care due to limited resources, a high
19 burden of HIV infection and a delay in recognizing complications may be reasons for the increased
20 incidences

21

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

1 low resource settings. In Africa the most common aetiologies include uterine rupture, atonic uteri and
2 sepsis (14,19,29-31).

3

4 Three studies performed in tertiary care settings in South Africa have shown particularly high rates of
5 sepsis. A study performed in Mthatha showed uterine atony, puerperal sepsis and secondary
6 postpartum haemorrhage made up 57% of the indications. The morbidly adherent placenta was the
7 least common indication (9). In a review of cases from Durban, uterine rupture and sepsis made up
8 56% of the indications (29) and a study from Pretoria reported that puerperal sepsis was the second
9 most common indication after ruptured uteri and accounted for 33% of peripartum hysterectomies
10 (31).

11

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

16

17 **MATERIALS AND METHODS**

18 A retrospective audit was performed at Tygerberg Hospital, a state academic referral center over a
19 five year period from February 2009 to March 2014. The study was approved by the local ethics
20 committee (S13/08/155). Cases were identified in theatre record books and individual case records
21 were reviewed. Data was extracted and transferred to an MS Excel spread sheet. The inclusion criteria
22 were all peripartum hysterectomies performed from a gestational age of 24 weeks until six weeks
23 postpartum. Information on patients age, gravidity, parity, gestation, HIV status, CD4 count, ARV
24 usage, medical history, past obstetric history, antenatal care and complications, intrapartum course,

1 mode of delivery, intrapartum complications, postpartum complications, neonatal outcome, indication
2 for hysterectomy, type of hysterectomy, surgical complications, estimated blood loss, high care
3 admissions, blood products required, morbidity, mortality and length of hospital admission was
4 collected.

5

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

10

11 **RESULTS**

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

20

21 Of the 160 cases that met the inclusion criteria nine individual case records were unavailable. Two of
22 these women demised and seven were discharged. One hundred and fifty one cases were therefore
23 included in the analysis. Ninety-six of these women delivered at Tygerberg Hospital and 55 delivered
24 at a referral center and were transferred due to complications. During this time period there were 34

1 558 births at Tygerberg hospital, giving an overall rate for peripartum hysterectomies at our institution
2 of 2.77 per 1000 deliveries.

3

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

11

12 Fifty women (33.3%) were HIV positive. Thirty-three (66%) were on antiretroviral treatment and 18
13 (40%) had a CD4 count less than 350 when they first presented for antenatal care. During the time
14 period of this study women were initially only started on lifelong antiretroviral treatment if their CD4-
15 count was less than 350. In July 2013 our national guidelines regarding antiretroviral treatment in
16 pregnant women changed. Since then all HIV-positive pregnant women are started on lifelong
17 antiretroviral treatment at their first antenatal visit. Other antenatal complications are documented in
18 table I.

19

20 One hundred and two patients attempted a vaginal delivery. Twenty-eight delivered vaginally (17.9%)
21 with one requiring an assisted ventouse delivery. Seventy women (46.4%) went into spontaneous
22 labour and 32 (21.2%) were induced. Indications for induction of labour are documented in table II.
23 Only seven patients had a successful induction that resulted in a normal vertex delivery. The reasons
24 for unsuccessful induction are detailed in table III.

1

2 One hundred and twenty three women (81.4%) had a caesarean section. Twenty-seven (22%) were
3 elective and 96 (78.1%) were emergency procedures. The indications for caesarean section are
4 documented in table IV.

5

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

18

19 Uterine atony was the second most common aetiology. Of the 24 (15.9%) peripartum hysterectomies
20 performed for uterine atony six patients (25%) were multigravidas, four (16.66%) had a multiple
21 pregnancy, two (8.33%) had macrosomic fetuses (estimated fetal weight more than 4kg) and eight
22 (33.33%) had a previous caesarean section. Eight (33.33%) had a vertex vaginal delivery and 16
23 (66.66%) had a caesarean section with eight (33.33%) being elective for previous caesarean
24 section(s), multiple pregnancy, breech presentation and suspected fetal macrosomia. Eight were
25 emergency caesarean sections. Eleven women (45.83%) went into spontaneous labour and five

1 (20.83%) had an induction of labour. Oxytocin infusion with artificial rupture of the membranes was
2 the induction method most commonly used. Four of the five patients who had inductions received
3 more than one induction method.

4

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

11

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

17

18 Uterine rupture occurred in eight cases (5.2%). Half of these women had previously delivered by
19 caesarean section. One woman needed a hysterectomy after blunt abdominal trauma. She had a
20 scarred uterus from a previous caesarean section and was 30 weeks pregnant. Three women went into
21 spontaneous labour and four had an induction of labour of which three received misoprostol and one
22 received prepidil and a balloon catheter.

23

1 Seven women (4,6%) who had a caesarean section for placenta praevia required a peripartum
2 hysterectomy for placental bed bleeding that was not controllable with conservative methods.

3

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

6

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

11

12 There were 6 cases of maternal deaths. We were unable to obtain the case records for 2 of these cases
13 but the cause of death on the death certificate was reported to be septic shock. Sepsis was therefore
14 the cause of death in five cases and hypovolemic shock in one case. Of the three cases whose deaths
15 were related to sepsis, where the clinical records were available, only one was HIV positive. She was
16 a 26 year old with a CD4-count of 17, not on antiretroviral treatment and who was known to have
17 chronic hepatitis B infection with liver failure as well as a history of perforated peptic ulcer disease.
18 She had a preterm vaginal delivery, complicated by disseminated intravascular coagulation (DIC) and
19 multiple postpartum haemorrhages requiring repeated laparotomies and transfusions. She developed
20 severe puerperal sepsis and had a septic uterus at the time of hysterectomy. She demised after she had
21 received 70 units of packed red blood cells, 71 units of fresh frozen plasma, 7 units of platelets and 7
22 units of cryoprecipitate during her hospital admission. The second was a 41 year old multigravida
23 who did not receive any antenatal care. She had a vaginal delivery at term and presented in septic
24 shock 3 days postpartum. She had a cardiac arrest and was successfully resuscitated but sadly demised
25 later that day. The post-mortem examination confirmed active pelvic floor sepsis and tonsillar

1 herniation due to brain oedema. The third woman was a 33 year old who was induced at 38 weeks for
2 hypertension. She had prolonged rupture of membranes and a caesarean section was performed for
3 fetal distress. One week postpartum she presented in septic shock. At the referring hospital she
4 suffered a cardiac arrest and was successfully resuscitated. A laparotomy was performed and a
5 ruptured sigmoid colon was repaired. A repeat laparotomy was required as she was unresponsive to
6 therapy and a total abdominal hysterectomy was performed. She later demised due to neutropenic
7 septic shock that was unresponsive to treatment. The maternal death related to haemorrhage and
8 hypovolemic shock involved a 19 year old primigravida who was induced for a post-date pregnancy
9 and received misoprostol followed by a balloon catheter. The membranes were then artificially
10 ruptured and oxytocin was given. A caesarean section was performed for poor progress. At caesarean
11 section an atonic uterus was diagnosed. She received ergometrine, prostaglandin F_{2α} and oxytocin.
12 Uterine compression sutures and uterine artery ligation were performed without success. The
13 abdomen and pelvis were then packed with swabs and she was transferred to Tygerberg Hospital. She
14 suffered a cardiac arrest during the surgery and was successfully resuscitated. Unfortunately DIC
15 developed and after two further laparotomies she demised.

16

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

20

21 43 women (28.66%) required one or more repeat laparotomies with one patient requiring nine relook
22 procedures. 137 women (90.41%) required blood transfusion. The average (median) amount of
23 packed red blood cells was six units with a range of 1 to 70 units. Ninety-six women (63.58%) were
24 given fresh frozen plasma. The average amount of fresh frozen plasma required was four units with a
25 maximum of 71 units. Fifty-two women (34.44%) required platelets. On average one pool of platelets

1 was required with a maximum of 7 units being used. Twenty-six patients (17.22%) required
2 cryoprecipitate.

3

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

10

11 **DISCUSSION**

12 Sepsis is an important aetiology for a peripartum hysterectomy, particularly in Southern Africa. In this
13 study, sepsis was the most common indication for a peripartum hysterectomy. This is the first study,
14 according to our knowledge, to report this finding. The high rate of sepsis may be due to the high
15 incidence of HIV infection in our community, low socio-economic standards, limited access to health
16 care, late diagnosis of complications, sterility issues in the labour ward and theatre and differences in
17 the definition and inclusion criteria used for peripartum hysterectomies. If the definition for
18 peripartum hysterectomies had been a hysterectomy at delivery or within 24 hours of delivery, or a
19 hysterectomy for uncontrolled haemorrhage we would have had no cases of sepsis and the incidence
20 in this study would have been significantly lower. Defining a peripartum hysterectomy as a
21 hysterectomy performed within 6 weeks of delivery, which is in line with the World Health
22 Organisation's (WHO) definition of maternal mortality(32), would result in more standard reporting
23 enabling one to compare studies with greater accuracy. Some may argue that even hysterectomies due
24 to miscarriages and gestational trophoblastic disease should be included in the definition as these are
25 also related to pregnancy. Improving access to antiretroviral treatment is important as all the women

1 who were HIV positive who needed a hysterectomy for the indication of sepsis had a CD4 count less
2 than 350 or where not using antiretroviral treatment. By implementing the WHO treatment program
3 Option B+, which entails starting a single daily dose fixed combination regimen for all HIV-positive
4 women irrespective of the CD4 count and the stage of disease (33), may decrease the rate of sepsis.

5

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

14

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

18

19 This study highlights the high morbidity and mortality associated with a peripartum hysterectomy.
20 Morbidity and mortality after a peripartum hysterectomy is high and the majority of deaths were
21 associated with sepsis. This is particularly challenging as the majority of septic hysterectomies occur
22 in countries that have limited access to high care and intensive care facilities.

23

1 Strengths of this study include the size of the sample and the definition used which includes
2 all hysterectomies performed until 42 days postpartum and does not limit the inclusion to
3 only hysterectomies for uncontrolled bleeding. Disadvantages of the study include that it was
4 a retrospective review.

5

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

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

11

12 **ACKNOWLEDGEMENTS**

13 None

14

15 **CONFLICT OF INTEREST**

16 None

17

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1 Tables

2 Table I: Antenatal complications

	Number of patients (n 151)	Percentage of patients (%)
Hypertensive related disorders	49	32.45
Hypertension	17	11.64
Pre-eclampsia	19	13.01
Pre-eclampsia with HELLP syndrome	13	8.9
Diabetes Mellitus	5	3.42
BMI > 40	14	9.59
PROM	6	4.11
APH	15	10.27
Antenatal sepsis	0	0
HIV	50	33,33%

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1 Table II: Induction of Labour: Indications

	Number induced (n 32)	Percentage of total inductions (%)
Hypertensive diseases of pregnancy	17	53.1
Hypertension	3	9.4
Pre-eclampsia	11	34.4
Eclampsia	3	9.4
Intra-uterine fetal demise	5	15.6
Postdate pregnancy	4	12.5
Prolonged rupture of membranes	3	9.4
Previous abruptio placenta	2	6.3
Previous intra-uterine fetal demise	1	3.1

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1 Table III: Reasons for unsuccessful inductions

	Number (n 32)	Percentage of total inductions (%)
Fetal distress	8	25
Not progressing to active labour	7	21.9
Poor progress during labour	4	12.5
Cephalo-pelvic disproportion	3	9.4
Uterine rupture	2	6.3
Extra-uterine pregnancy	1	3.1

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1 Table IV: Indications for Caesarean section

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

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