THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

EPIDEMIOLOGY OF ECTOPIC PREGNANCY AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA

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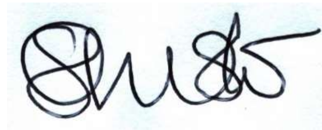

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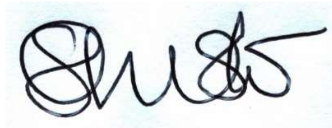

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ABSTRACT

Background: Ectopic pregnancy is defined as a pregnancy outside the uterine cavity and is a life-threatening emergency in the field of obstetrics and gynaecology. It is a most common cause of maternal morbidity and mortality in the first trimester of pregnancy. In resource-constrained settings, where trained specialists are limited in number and geographic location, outcomes are worse. Diagnosis is frequently missed, partly because the patient may not be aware that she is pregnant. However, timely diagnosis accompanied by appropriate management of ectopic pregnancy can alter the clinical course from death to life. The study aims to determine the epidemiology of ectopic pregnancies at University Teaching Hospital (UTH).

Methods: A cross sectional study conducted between May, 2014 to November, 2014 in the Department of Obstetrics and Gynaecology at the University Teaching Hospital, Lusaka, Zambia. Women treated for ectopic pregnancies were recruited from the gynaecology ward, interviewed by research assistants and data abstracted from their medical files.

Results: A total of 90 women with ectopic pregnancies were enrolled representing 0.5% of early and late pregnancy admissions (total 19,600 pregnant women reviewed between May 2014 –November, 2014). Over 70% were from high residential areas, 52% had at least secondary education, and 81.1% were married or co-habiting. Although 27.8% were HIV positive, 37.8% did not have a known status. Almost half (46.6%) were in their first or second pregnancy. Though 10% were in the second trimester (13-19weeks) gestation, most (67.8%) were below 12 weeks and in 22% the gestation was not known. The commonest risk factors were: more than one sexual partner ever (55.6%) with 10% ever treated for a sexually transmitted disease. The commonest symptoms were lower abdominal pain (97.8%) and amaenorrhea (83.3%). Dizziness was reported in 48.9%. About a quarter (24.4%) were considered in shock on admission and most had abdominal tenderness (86.7%). Where an ultrasound was done (n=57, 63.3%) this was helpful in 86% of cases (n=49). Haemoperitnem was reported in 59.6%. In 65 cases (72.2%) either paracentesis or culdocentesis was done and was positive for blood in 49 (75.4%) of cases. Apart from only one case treated with methotrexate, all other had a laparotomy and 70% were found ruptured. The commonest sites for the ectopic were infundibulum (33.3%) and ampulla (28.9%). Salpingectomy was the commonest procedure (84.4%). Over half (54.3%) had blood loss greater than 500mls. And 44 (48.9%) were transfused. In 34 cases of those transfused, one or two units were transfused. Four patients (4.4%) were recovered in a high dependency unit – the rest in an ordinary ward. One patient died (case fatality of 1.1%).

Conclusion: The series at UTH showed that ectopic pregnancy had a low prevalence and had a risk factor profile and clinical presentation like that described elsewhere in the region. Most cases presented with a ruptured ectopic requiring blood transfusion. Earlier presentation can provide an opportunity for more conservative treatment with less morbidity.

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ABBREVIATIONS

HCG- Human Chorionic Gonadotrophin

ICU- Intensive Care Unit

MMED-Master of Medicine

SPSS- Statistical Analysis for Social Sciences

SOU- Special Observation Unit

UTH- University Teaching Hospital

DEDICATION

This dissertation is dedicated to my wife Naomi Choshi Kasanda, my daughter Phoebe Choshi Chisha and my sons Phillip Sume and Ethan Hezekiah

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1. INTRODUCTION

Defined as a pregnancy outside the uterine cavity (Cunningham, 2005), ectopic pregnancy is a life-threatening emergency in the field of obstetrics and gynecology. It is the most common cause of maternal morbidity and mortality in the first trimester of pregnancy (Okunlola et al, 2006). In resource-constrained settings, where trained specialists are limited in number, outcomes are worse (Nwagha et al, 2007). Diagnosis is frequently missed, partly because the patient may not be aware that she is pregnant (Houry, 2007). However, timely diagnosis accompanied by appropriate management of ectopic pregnancy can alter the clinical course from death to life.

There is currently an increased global incidence of ectopic pregnancy. Several studies in developed countries show increased incidence of ectopic pregnancy (Trabert et al, 2011; Stulberg et al, 2013; Rajkhowa et al, 2000), which may be attributable to rising prevalence of risk factors and advanced diagnostic methods (Jurkovic, 2007). On the other hand, health care workers in resource-limited settings are challenged by late presentations with rupture in more than 80% in most cases (Igbarese et al, 2005). Poor diagnostic tools and limited capacity to handle emergencies result in increased maternal morbidity and mortality and reproductive failure (Udigwe et al, 2010). The unruptured ectopic pregnancy may be intact, or slowly leaking, and thus evade early diagnosis. The rupture can occur early in the gestation, potentially eliminating the option of conservative treatment (Fylstra, 2002).

With such potential differences between developed and developing countries regarding ectopic pregnancy, local data are important. In the region of Southern Africa, published data regarding ectopic pregnancies are sparse. A South African study showed a high incidence of HIV infection in women admitted to the hospital for ectopic pregnancy, abortions, or pelvic inflammatory disease (Wilkinson et al, 1999). A cross-sectional study at Umtata General Hospital in South Africa from almost 20 years ago revealed that 62.2% of 148 ectopic pregnancies presented in shock and with severe anaemia (Amoko et al, 1995). Furthermore, about 86% of cases were associated with pelvic inflammatory disease (Amoko et al, 1995). When focusing on published data from Zambia, the literature is limited to case reports, most of which are dated 1990 or earlier. Case reports notable are those done by Nova et al (2005) and Mkandawire (2010).

Statement of the Problem and Study Justification

Statement of the problem:

An audit of UTH gynaecology records for 2012 showed that 197 ectopic pregnancies out of 6566 (i.e. 3%) gravid patients were admitted. Most of the patients present to gynecology emergency care in shock and ended up with laparotomy and salpingectomy with several days of post-operative care. Epidemiological findings, clinical presentation and outcome of patient with ectopic have not been documented locally hence the need to conduct this study.

Study justification

There is a critical gap in the current, local literature regarding ectopic pregnancies. This study will address this gap in developing locally relevant protocols to diagnose ectopic pregnancy in a timely manner to mitigate maternal morbidity and mortality.

Research Question

What is the epidemiology of ectopic pregnancy in patients presenting at UTH?

Objectives

Main objective:

To determine the epidemiology of ectopic pregnancies at UTH

Specific objectives:

1. Determine the prevalence of ectopic pregnancies
2. Determine social demographic factors associated with ectopic pregnancies
3. Describe the common clinical presentation
4. Describe the management and outcome.

2. LITERATURE REVIEW

Prevalence and incidence of ectopic pregnancy

Prevalence

The worldwide estimated prevalence is 1-2 % (Jurkovic, 2011) and in Africa, ranges from 1% (rural) to 13% (urban) (Kaplan et al, 1996). In Nigeria, 4.3% prevalence (Yakasa, 2012). Locally in Zambia there are no statistics available**.**

Incidence

There are different hospital-based studies on ectopic pregnancy in Africa and other resource-limited settings. The incidence of ectopic pregnancy varies from country to country, and within the same country, it varies from one community to another. The incidence of ectopic pregnancy depends on the population studied and ranges from 1% in rural general practice to 13% in urban emergency department (Kaplan et al, 1996). Many studies on ectopic pregnancy are carried out in government hospitals; hence, the true picture of incidence may be underestimated, as those seen in the private hospitals are not included. In addition, some women may die at home because many people seek medical care late.

The global incidence of ectopic pregnancy is currently increasing. This incidence may be related to a higher incidence of tubal disease, notably salpingitis. Other reasons for the rising incidence of ectopic pregnancy are pelvic inflammatory disease, intrauterine contraceptive device, surgical procedures for tubal disease, and improved diagnostic technique (Arup et al, 2007). The overall incidence of ectopic pregnancy is rising in many countries, depending on the prevalence of risk factors and the methods of diagnosis available (Jurkovic, 2007).

The incidence of a simple ectopic gestation varies from 1 in 300 pregnancies in Europe to as high as 1 in 20 to 50 pregnancies in Africa and the West Indies (Piam & Otubu, 2006).

The incidence of recurrent ectopic pregnancy is approximately 15% and rises to 30% following two previous ectopic pregnancies (Tulandi, 1988). A figure of 1 in 4000 to 7000 pregnancies is currently quoted for heterotopic gestation (Jurkovic, 2007). Heterotopic pregnancies used to be extremely rare with only a few case reports (DeVoe & Pratt, 1998), but are now estimated at_1-3% of all pregnancies and 10-15% of all ectopic pregnancies following in vitro fertilization and embryo transfer (Aliyu et al, 2008).

Despite the continued increase in the incidence of ectopic pregnancy, the rate of death from ectopic pregnancy has declined in developed countries, primarily because of earlier diagnosis before tubal rupture (Jurkovic, 2007). Modern diagnostic methods are used to diagnosis ectopic pregnancies quickly in over 70% of cases in developed countries (Rajkhowa et al, 2000).

In recent decades, most methodological limitations in various African published literatures make it impossible to draw formal conclusions concerning the incidence of ectopic pregnancy in Africa (Goyaux et al, 2003). In African developing countries, most hospital-based studies have reported ectopic pregnancy case fatality rates of around 1-3%, ten times higher than that reported in industrialized countries (Goyaux et al, 2003). Late presentation to the health facility, late diagnosis leading in almost all cases to most complications, and emergency surgical treatment are the key factors accounting for such high fatality rates in women suffering from ectopic pregnancy in Africa. The incidence of ectopic pregnancy was found to be 0.79% in Yaoundé, Cameroun (Leke et al, 2004). This value may be considered a minimum due to probably underestimation. Nevertheless, this rate is lower than currently observed in industrialized countries.

The late diagnosis, low percentage of women receiving conservative treatment and subsequent maternal deaths are important findings that should encourage gynaecologists working in Africa to promote ectopic pregnancy prevention programs and to improve the care given to women with ectopic pregnancies. The case fatality rate of ectopic pregnancy in Ghana was found to be 27.9/ 1000 (Baffoe & Nkyekyer, 1999).

A study conducted in 1992 and 1993 at the Umtata General Hospital in Transkei, South Africa reported an ectopic pregnancy incidence of 1.1% (Amoko et al, 1995). Between the years 1993 to 1995, the hospital based ectopic pregnancy incidence at Nosy Be Hospital, Madagascar was 2.9% (Ratinahirana et al, 1997). It was 4% at the gynaecology and obstetrics clinic of the national teaching hospital in Cotonou Republic of Benin (Perrin et al, 1997).

Ectopic pregnancies are an important cause of maternal death in developing countries. A previous study on the incidence of ectopic pregnancy done at Benin City, Nigeria revealed an incidence of 3.5%. In Marked, Nigeria, ruptured tubal pregnancy accounted for 0.87% of all fetal births and 94.6% of all ectopic pregnancies. There was a rising trend in the incidence of ruptured tubal pregnancy from 0.65% in 2004 to 1.09% in 2006 (Jogo & Swende, 2008). These observations suggest that the incidence of ectopic pregnancy in developing countries especially on the African continent has probably increased in the recent decades (Thonneau et al, 2002).

Clinical presentation

The common symptoms of women who present with ectopic pregnancies are amenorrhea, per vaginal bleeding, anaemia, hypotension and abdominal pain, in other cases, ectopic pregnancies may be terminated spontaneously before they give rise to notable clinical symptoms. A study by Jabbar (1980) revealed that 95% of patients had amenorrhea and abdominal pain as presenting signs and symptom. s

From the International Journal of Gynecology and Obstetrics (Lindow, 1988) a prospective study of 100 consecutive ectopic pregnancies treated at South Africa's Edendale Hospital in 1983-84 was undertaken to assess the clinical mode of presentation, the reliability of available diagnostic aids such as colpopuncture, and any concurrent pathology. Beta human chorionic gonadotropin (HCG) was not available at this facility and ultrasound was performed by untrained personnel, if at all; diagnostic colpopuncture was the major diagnostic method in cases of ectopic pregnancy. The main clinical features noted in this series of patients were: amenorrhea (91%), infertility of a duration exceeding 2 years (61%), abnormal vaginal bleeding (49%), shoulder tip pain (33%), a history of pelvic inflammatory

disease (32%), and pain on defecation (26%). Diagnosis of ectopic pregnancy was confirmed by colpopuncture in 69% of cases.

Furthermore, a cross-sectional study (Amoko, 1995) was done on clinical presentation of ectopic pregnancy in Transkei, South Africa at Umtata General Hospital, which serves an underprivileged black South African population, the incidence of ectopic pregnancy was 11 per 1000 reported pregnancies, and the mortality rate was 2.0%. Of 148 consecutive cases of ectopic pregnancy, 62.2% were in shock and two thirds were severely anaemic on arrival. About 71% of the cases had tubal rupture and 25% were chronic leaking ectopic. Only four intact unruptured ectopic pregnancies were found despite the availability of modern diagnostic techniques such as ultrasonography and sensitive pregnancy tests. The conclusion was that most ectopic pregnancies in Transkei are associated with previous pelvic infection, and presented as acute emergencies in shock and with anaemia.

In summary, the above studies reviewed that the most common symptoms were amenorrhea (91%) (Lindow, 1988), 95 %(Jabbar, 1980) and shock /anemic (62.2%) (Amoko, 1995)

Risk factors

Multiple factors contribute to the relative risk of an ectopic pregnancy. Despite this, some patients that may not have any risk factors do develop an ectopic pregnancy. In theory, any occurrence that hampers or delays the migration of the embryo to the endometrial cavity could predispose women to ectopic pregnancy. Age, marital status, and parity have not been found to be significant risk factors for ectopic pregnancy (Anorlu et al, 2005). The reported aetiological factors for ectopic pregnancy include pelvic inflammatory disease, post-abortal sepsis, postpartum sepsis, previous ectopic pregnancy, reversal of previous tubal sterilization, tubal spasm, long defects of the fallopian tubes and psychological and emotional factors (Doyle et al, 1991).

Pelvic inflammatory disease from inappropriate obstetric care or from unsafe abortion is a risk factor for ectopic pregnancy. This infection causes distortion in the genital tract and the fallopian tube. Unsafe abortion will also lead to post-abortal sepsis. Induced abortion and sexually transmitted disease increases the risk four-fold and

nine-fold respectively (Anorlu et al, 2005). In addition, multiple sexual partners predispose the patient to acquiring sexually transmitted diseases. Pelvic inflammatory disease is a major risk factor for developing ectopic pregnancy in Nigeria (Olarewaju, 1994; Egwuatu & Ozumba, 1987). In a study in France (Coste et al, 2003) found that *Chlamydia trachomatis* seropositivity appeared to be an important risk factor in the development of ectopic pregnancy.

Biologically, the adolescent is particularly at risk of sexually transmitted disease because of the histology of the genital tract. Columnar epithelium, which is susceptible to *Chlamydia* and *gonococci* organism extends from the endocervical canal to the ectocervix making it fully exposed to pathogens. Adolescents also lack immunity to certain pathogens. Early sexual debut may also lead to adolescent pregnancy which is often unwanted and which usually results in induced abortion conducted in unsafe places and by incompetent or poorly trained individuals. Late age of sexual debut on the other hand, significantly reduces the risk of ectopic pregnancy (Anorlu et al, 2005).

Induced abortion as a significant risk factor for ectopic pregnancy was not observed in studies from countries where abortion is legalised (Atrash et al, 1997). This is because qualified medical personnel carry it out under aseptic conditions in a sterile environment and with sterile instruments.

Ectopic pregnancy is one of the recognised complications of in-vitro fertilization and embryo transfer (Okohue et al, 2010). Ectopic pregnancy can present following an in vitro fertilization procedures. A high index of suspicion is necessary even in cases with previous bilateral salpingectomies or easy embryo transfer. A case control study conducted showed that the risk of ectopic pregnancy was increased four -fold with induction of ovulation (Fernandez et al, 1991).

The use of intrauterine contraceptive devices increases the risk of developing an ectopic pregnancy by almost four-fold (Anorlu et al, 2005).

Previous history of an ectopic pregnancy increases the risk for another ectopic pregnancy. The risk of recurrent ectopic pregnancy is 12-18% (Jurkovic, 2007). Every woman with a previous ectopic pregnancy would be at a high risk of recurrence of

another ectopic pregnancy. This should be excluded when a patient with a previous ectopic pregnancy presents in early pregnancy.

Scarring following tubal surgery causes anatomical abnormalities of the fallopian tube, which presents with abnormal embryo transport and increases the risk of ectopic pregnancy (Doyle et al, 1991). However, there are reports of ectopic pregnancies implanting on previous caesarean section scars. Endometrial and myometrial disruptions or scaring can also predispose to abnormal implantation or abdominal pregnancy (Fylstra, 2002).

3. METHODOLOGY

Study design

This was a cross-sectional study.

Study site

The study was carried out at the Department of Obstetrics and Gynaecology at UTH, in Lusaka Zambia.

Target population

All patients who presented to Gynecological and/or Surgical wards and suspected of having an ectopic pregnancy.

Study population

Patients who were managed with a diagnosis of ectopic pregnancy who met eligibility criteria

Inclusion criteria

- Being managed as an ectopic pregnancy
- Able to provide consent (for those 18 years old and under, guardian consent was obtained and assent obtained from the patient)

Exclusion criteria

- Patients refusing to consent

Study duration

Recruitment took six (6) months from May 2014 to November 2014.

Sampling methods

Convenience sampling was used to enroll every eligible patient.

Sample size

The following prevalence sample size equation was used to determine sample size for this study.

$$N = \frac{Z^2 x\, PQ}{D^2} = \frac{Z^2 x\, P\,(1-P)}{D^2} \qquad \text{where } Q=1-P$$

- z=confidence level at 95% (standard value of 1.96)

- d=specific margin of error at 5% (standard value of 0.05)
- p= estimate of population with characteristic of interest: 5%.

Assuming 5% (with a confidence limit of +/- 5 %) is the prevalence of ectopic pregnancies in Africa at 95% power and alpha of 5%, the sample size came to 73 participants. With an allowance of 20 % (approximately 15) lost to follow up, the total sample size was 88. For this study, a total of 90 patients were enrolled as these were all the patients that presented in the study period

Participant recruitment

Written informed consent was sought from the women before being recruited in the study. If unable to read or write her name, a witness was present when the participant used a thumbprint instead of her signature. See Appendix 1.

Data collection

Before being discharged from the ward, patients treated for ectopic pregnancies were interviewed by research assistants as well as data extracted from their medical records/files. The data was collected using a standardized structured questionnaire (Appendices 2 and 3). Errors were minimized double entry and using range and consistency checks.

Data Analysis

All data collected was entered an Excel spreadsheet and imported to SPSS version 14 for analysis. The analysed univariate data is presented as frequency distributions, or mainly as percentages or proportions corresponding to categories previously described. In addition, some data are illustrated as bar graphs. Most continuous variables were categorised into pre-determined categories and some presented as means and/or medians and percentages.

Operational definition of variables

Variables	Continuous or categorical	Notes
Age of mother	Continuous	May subsequently be categorised into discrete categories (e.g. 15-24,24-34,35-44)
Gestational age of ectopic pregnancy	Continuous	May subsequently be categorised into discrete categories (e.g. <12,12-15, ≥16)
Gravidity	Continuous	May subsequently be categorised into discrete categories (e.g.1, 2-5, 6-9,>9)
Parity	Continuous	May subsequently be categorised into discrete categories (e.g.0,1-4,5-8,>8)
Mode of diagnosis	Categorical	Categorised as clinical, ultrasound, laparotomy
Site of ectopic pregnancy	Categorical	Categorized as cornua, interstitial, ovary, ampulla, infundibulum, mesentery, bowel
Length of hospital stay, if applicable	Continuous	May be subsequently categorised into discrete categories (e.g. <3,4-6,7-10, ≥10)
Admission to high dependency unit	Categorical	Categorised as yes (SOU), yes (Annex), yes (main ICU), or no
Vital status at discharge from hospital	Categorical	Categorised as alive or dead

Ethical considerations and Permissions:

Ethical approval was obtained from the ERES Converge IRB (Appendix 4). Eligible participants were enrolled in the study only after obtaining informed consent by either a signature or a thumb print. Participants were fully informed of the study in a language they understood and participant confidentiality was maintained throughout the study by ensuring data collection instruments had no personal identifiers and were kept in a locked cabinet.

4. RESULTS

4.1 Prevalence of Ectopic Pregnancy

A total of 90 patients with ectopic pregnancy were enrolled. The institutional pregnancy admissions (both early pregnancy and obstetric) was 19,600 giving a prevalence 0.05%. Ideally, we would have needed all pregnancies in Lusaka to be able to give a truer prevalence.

4.2 Socio-Demographic Characteristics

Table 1 summarises the demographic characteristics of patients with ectopic pregnancy. Specific characteristics are outlined as follows:

Age

The patient age distribution is shown in figure 1. The mean age was 29 years (SD = 5.7). The minimum age was 18 years and maximum 39 years.

Figure 1: Frequency distribution of age (n=90)

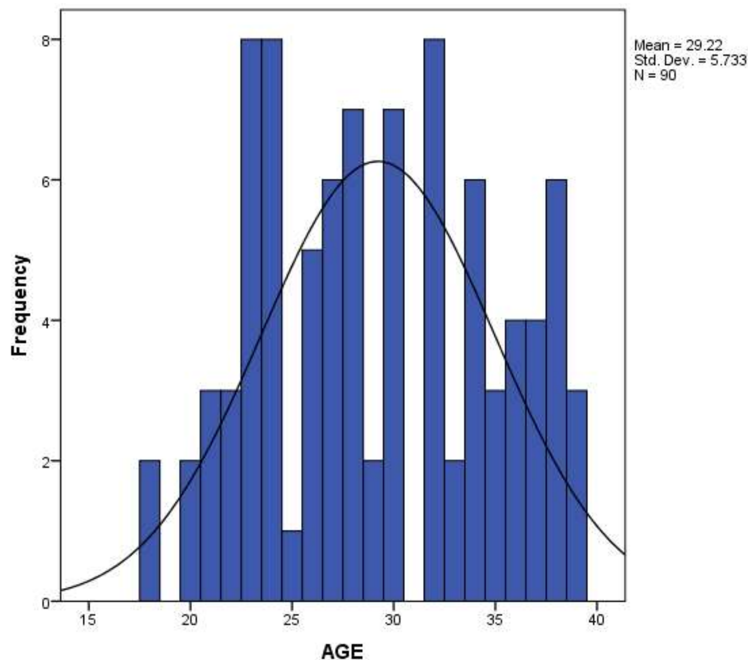


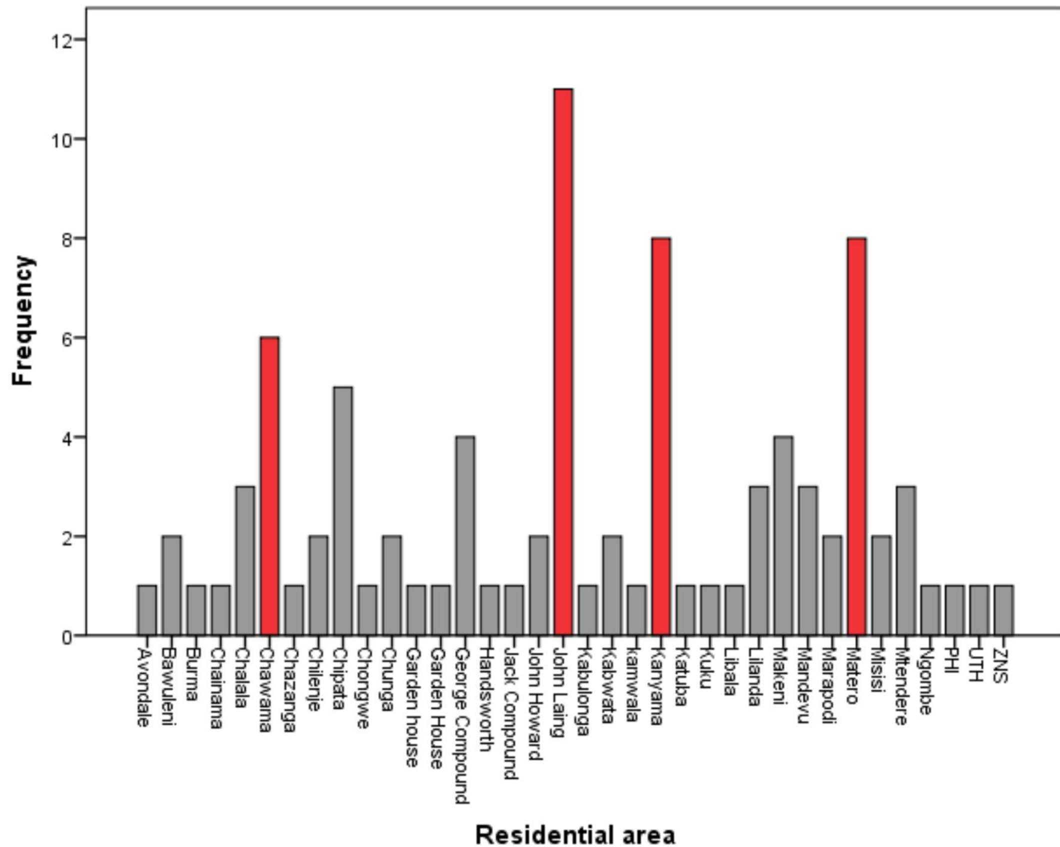
Table 1. Demographic characteristics of patients with ectopic pregnancy (n=90)

Variable	n	percent
Age		
15-19	2	2.2
20-24	24	26.7
25-34	44	48.9
35 or more	20	22.2
mean 29 years (SD = 5.7). Minimum 18 years and maximum 39 years.		
Residence		
High density	64	71.1
Medium density	16	17.8
Low density	6	6.7
Peri-Urban	4	4.4
Education		
None	2	2.2
Primary	32	35.6
Secondary	46	51.1
Tertiary	10	11.1
Monthly Household Incomes	**n**	**%**
1. < 500.00 k	0	0.0
2. 500.00 - 2,000.00 k	56	62.2
3. 2,000.00 - 5,000.00 k	9	10.0
4. 5,000.00 - 15,000.00 k	2	2.2
5. > 15,000.00 k	0	0.0
6. Unknown	23	25.6
Marital Status	**n**	**%**
1. Single/never married	14	15.6
2. Married/cohabiting	73	81.1
3. Divorced/widowed	2	2.2
4. Unknown	1	1.1

Residential area

Over 70% were from high density areas and the actual areas are outlined in figure 2.

Figure 2: Frequency distribution of residential area (n=90)



Education

At least 52% of the women had secondary level education and another 11.1% had tertiary education.

Monthly Household Income

Most the patients 56/90 (62.2%) had household income in the range K500 – K2, 000.

Marital Status

Most women were married or co-habiting (81.1%) though a sizeable proportion (15.6%) were single.

4.3 Early Pregnancy History

The early pregnancy history of patients with ectopic pregnancy is outlined in table 2.

Whereas 27/8% of patients with ectopic were HIV positive, about a third (34.4%) were negative though a larger proportion had unknown status (37.8%). The gravidity and parity of the 90 patients showed that a significant minority were in their first pregnancy (12.2%) thought he highest proportion of gravidity was in those gravida 2 (second pregnancy). The majority were below 12 weeks gestation, though it was unknown in 22.2%. Hardly any had started antenatal care yet (93.3%).

Table 2. Early pregnancy history of patients with ectopic pregnancy (n=90)

Variable	n	percent
HIV Status	**n**	**%**
1=Reactive,	25	27.8
2=Non-reactive,	31	34.4
3=Unknown	34	37.8
Gravidity	**n**	**%**
1	11	12.2
2	31	34.4
3	20	22.2
4	13	14.4
5 or more	14	15.6
unknown	1	1.1
Parity	**n**	**%**
0	13	14.4
1	31	34.4
2	17	18.9
3	13	14.4
4	6	6.7
5 or more	9	10.0
unknown	1	1.1
Gestational age based on LMNP	**n**	**%**
<6wks	20	22.2
6,7,8,	24	26.7
9, 10, 11,12	17	18.9
13-19	9	10.0
unknown	20	22.2
Receiving antenatal care	**n**	**%**
No	84	93.3
Yes	5	5.6
unknown	1	1.1

4.4 Risk Factors

Table 3 lists the most common risk factor was ‘having more than 1 sexual partner ever (one sexual partner at one given time)’ with 50/90 (56%) and ‘multiple sexual partners at one time ever’’ (multiple sexual partners at any given time) with 13/90 (14%).

Table 3. Risk factors for ectopic pregnancy (n=90)

Variable	n	percent
Treated for STI ever		
Yes	9	10.0
No	80	88.9
unknown	1	1.1
Treated for Vaginal Discharge Ever		
Yes	7	7.8
No	82	91.1
unknown	1	1.1
History of Unsafe Abortion Ever (a total of 79 with previous pregnancy)		
Yes	7	8.9
No	70	88.6
unknown	2	2.5
total	79	100.0
More Than 1 Sexual Partner Ever		
Yes	50	55.6
No	38	42.2
unknown	2	2.2
Multiple Sexual Partners Currently		
Yes	5	5.6
No	83	92.2
unknown	2	2.2
Multiple Sexual Partners Ever		
Yes	13	14.4
No	75	83.3
unknown	2	2.2
Assisted Conception (IVF, Clomifene) With This Pregnancy	**n**	**%**
Yes	2	2.2
No	87	96.7
unknown	1	1.1
Intrauterine Contraceptive Device (IUCD) Currently	**n**	**%**
Yes	1	1.1
No	89	98.9
Previous History of Ectopic Pregnancy	**n**	**%**
Yes	6	6.7
No	84	93.3
Previous History of Tubal Surgery	**n**	**%**
Yes	6	6.7
No	84	93.3

4.5 Clinical Presentation – Symptoms and Signs

Symptoms at Admission

The most common symptoms at admission (listed in table 4 and illustrated in figure 3) was lower abdominal or pelvic pain with 88/90 (98%) of the patients presenting with the symptom, followed by amenorrhea with 75/90 (83%). The least presenting symptom was pain while having bowel movement and shoulder pain with 11/90 (12%) and 12/90 (13%).

Figure 3: Frequency distribution of symptoms at admission (n=90)

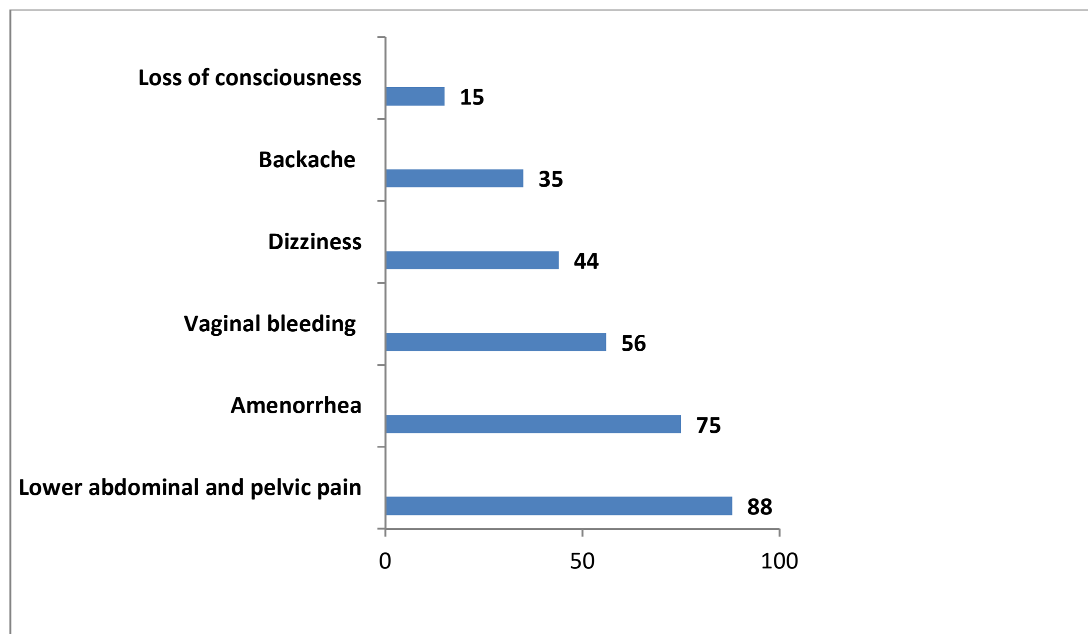


Table 4. Clinical presentation - history (n=90)

Variable	n	percent
History of amenorrhea		
Yes	75	83.3
No	15	16.7
Lower abdominal pain		
Yes	88	97.8
No	2	2.2
Backache		
Yes	35	38.9
No	55	61.1
Shoulder tip pain		
Yes	12	13.3
No	78	86.7
Vaginal bleeding		
Yes	56	62.2
No	31	34.4
unknown	3	3.3
Pain on defaecation		
Yes	11	12.2
No	78	86.7
unknown	1	1.1
Dizziness		
Yes	44	48.9
No	43	47.8
Loss of Consciousness		
Yes	15	16.7
No	75	83.3

Examination findings on admission (signs)

About 11% of patients had a mean arterial pressure of <60 and clinically 24.4% were deemed to be in shock. Abdomino-pelvic tenderness was common (86.7%) though vaginal bleeding was only present in 43.3%. In only 70% was a pregnancy test done and in the remaining 30% the judgement was clinical.

Table 5. Clinical presentation – Examination (signs) (n=90)

Variable	n	percent
Admission BP (mean arterial blood pressure)		
>60 (all systolic >90mmHg)	73	81.1
<60 (all systolic <90mmHg)	10	11.1
missing	7	7.8
Clinician judgement that patient is in shock on admission		
Yes	22	24.4
No	64	71.1
unknown	4	4.4
Abdomino-pelvic tenderness on palpation		
Yes	78	86.7
No	6	6.7
unknown	6	6.7
Vaginal bleeding on examination		
Yes	39	43.3
No	27	30.0
unknown	24	26.7
Pregnancy test	**n**	**%**
done and positive	63	70.0
not done	27	30.0

4.6 Ultrasound Findings

An ultrasound was done in 57 of the 90 (63.3%) of patients and this helped in 86% of cases (49/57) (table 6). In almost 60% there was evidence of haemoperitoneum.

Table 6. Ultrasound findings (n=90)

Variable	n	percent
Ultrasound Done		
Yes	57	63.3
No	31	34.4
unknown	2	2.2
If Yes, Was Ectopic Pregnancy Diagnosed on Ultrasound	**n**	**%**
Yes	49	86.0
No	7	12.3
unknown	1	1.8
	57	100.0
If Yes, Was Haemoperitoneum In Douglas Pouch Reported on Ultrasound	**n**	**%**
Yes	34	59.6
No	18	31.6
unknown	5	8.8
	57	100.0

4.7 Culdocentesis and Paracentesis

Culdocentesis was done in 42 (46.7%) of cases (table 7). In just over three quarters of these (76.2%) the result was positive for blood. Paracentesis was done in 38 (42.2%). In over half of these (55.3%), the result was positive.

In 65 patients (72.2%) either paracentesis or culdocentesis was done and in 49 cases (75.4%) the result was positive. In cases where both ultrasound and paracentesis or culdocentesis were done, results were mixed.

Table 7. Culdocentesis and paracentesis findings (n=90)

Variable	n	percent
Culdocentesis Done	**n**	**%**
Yes	**42**	**46.7**
No	48	53.3
IF YES Blood on CULDOCENTESIS	**n**	**%**
Yes	32	76.2
No	10	23.8
Paracentesis	**n**	**%**
done	**38**	**42.2**
not done	52	57.8
Paracentesis Result	**n**	**%**
Positive	21	55.3
Negative	17	44.7
Either Culdocentesis Or Paracentesis Done	**n**	**%**
Yes	**65**	**72.2**
No	25	27.8
Culdocentesis or paracentesis result	**n**	**%**
Positive	49	75.4
Negative	16	24.6
In 41 cases both US and tap done; hemoperitoneum present?	**n**	**%**
yes / yes	19	46.3
yes / no	7	17.1
no / yes	10	24.4
no / no	5	12.2
	41	100.0

4.8 Mode of Treatment and findings

Table 8 lists the most common mode of treatment at admission was surgical via laparotomy with 88/90 (97.8%) patients only 1 (1.1%) was treated medically with methotrexate. In one case, the case notes were incomplete. The ectopic was ruptured in 70% of cases and over three quarters had evidence of haemoperitoneum. Salpingectomy was by far the commonest surgical procedure (84.4%). The commonest site of the ectopic was the infundibulum (33.3%) followed by the ampulla (28.9%). There was no heterotopic pregnancy observed. (Figure 4)

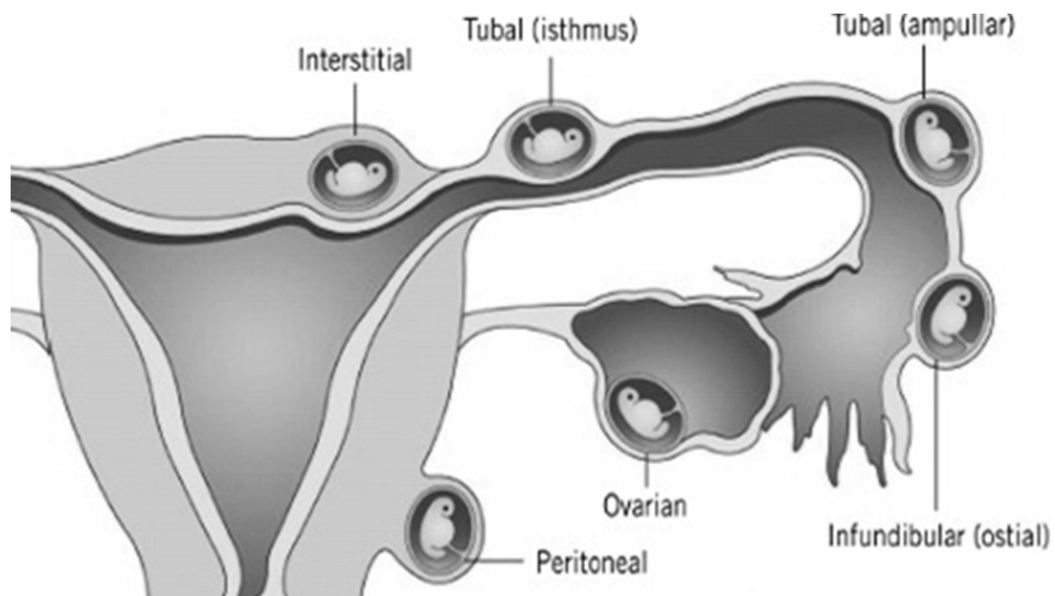


Figure 4: SITE OF ECTOPIC PREGNANCY

KEY TO SITE OF ECTOPIC	n	%
INFUNDIBULAR	30	33.3
AMPULLA	26	28.9
CORNUA	15	16.7
abdominal cavity	5	5.6
Isthmus	5	5.6
OVARY	4	4.4
CERVIX	2	2.2
UNKNOWN/NOT RECORDED	3	3.3

Table 8. Treatment and findings (n=90)

Variable	n	percent
Definitive Mode of Treatment of Ectopic Pregnancy	**n**	**%**
Surgical via Laparotomy	88	97.8
Medical with Methotrexate	1	1.1
Unknown/Not Recorded	1	1.1
If Surgery What Were Intraoperative Findings	**n**	**%**
Ruptured Ectopic Pregnancy	63	70.0
Unruptured Ectopic Pregnancy	13	14.4
Not Recorded	14	15.6
If Surgery, Was There Haemoperitoneum	**n**	**%**
Yes	70	77.8
No	1	1.1
Not Recorded	19	21.1
If Surgery, What Was the Procedure	**n**	**%**
Salpingectomy	76	84.4
Salpingo-Oophorectomy	5	5.6
Subtotal Hysterectomy	1	1.1
Unknown/Not Recorded	8	8.9
Site of Ectopic	**n**	**%**
Infundibulum	30	33.3
Ampulla	26	28.9
Cornua	15	16.7
Abdominal Cavity	5	5.6
Isthmus	5	5.6
Ovary	4	4.4
Cervix	2	2.2
Unknown/Not Recorded	3	3.3

4.9 Blood Loss (Haemoperitoneum)

Haemoperitoneum was present in 70/90 (77.8%) of cases but not recorded in case notes in 19 (21.1%). Table 9 tabulates the amount of haemoperitoneum. In 23 cases of the 70 (32.9%) there was loss between 500-1000mls. In 22 (31.4%) there was loss >1000mls. Blood was transfused in under half of cases (48.9%) and again half of the transfusions (22 of 44, 50%) were per-operative. Almost three quarters had between one and two units transfused.

Table 9. Blood loss and blood replacement (n=90)

Variable	n	percent
Amount of Haemoperitoneum (n=70)		
<200mls	8	11.4
200-500	17	24.3
500-1000	23	32.9
>1000	22	31.4
	70	100.0
Blood transfused?		
Yes	44	48.9
No	46	51.1
When transfused (n=44)		
Per-Operatively	22	50.0
Post-Operatively	9	20.5
Pre-Operatively	4	9.1
Unknown Timing/Location	9	20.5
	44	100.0
Amount of blood transfused		
1 unit	17	38.6
2 units	17	38.6
3 units	4	9.1
4 units	1	2.3
5 units	1	2.3
6 units	3	6.8
8 units	1	2.3
	44	100.0

4.10 Post-operative recovery and outcome

Having been admitted via the emergency ward, post-operatively, the majority were subsequently recovered in the general ward (93.3%) (table 10). Two cases (2.2%) were admitted to the intensive care unit and another two (2.2%) to a high dependency unit.

The mean duration from admission to discharge was 6.6 days with a median of 4 days. The minimum was 2 days and maximum 8 days.

Of the ninety (90) patients there was one (1) mortality making it 1 % case fatality case.

Table 10. Post-operative recovery and outcome (n=90)

Variable	n	percent
Admission to High Dependency Unit		
Yes, ICU	2	2.2
Yes, high dependency unit	2	2.2
No	84	93.3
Unknown	2	2.2
Outcome		
Alive	89	88.9
Died	1	1.1

5. DISCUSSION

According to the UTH Hospital records from May 2014 to November, 2014 in the Department of Obstetrics and Gynaecology the total number of patients recruited for the study were 90 against 19,600 pregnant women (early or late pregnancy) giving a prevalence rate of 0.05 %. Ectopic pregnancies are rare and this is in keeping with the worldwide estimated prevalence of 1-2 % (Jurkovic, 2011) and in Africa, ranging from 1% (rural) to 13% (Urban) (Kaplan et al, 1996).

The catchment area for University Teaching Hospital is the whole country but all the sampled 90 patients were Lusaka residents of which the majority from high density residential areas. Few patients from low density areas were attended to since their population is small and mostly these are well to do who seek medical care from private hospitals. The cases from private facilities were not captured by this study

The patient age distribution was approximately normally distributed with mean age 29 years (SD = 5.7). The minimum age was 18 years and maximum 39 years. The age range was within the reproductive age group in Zambia of 15 years to 49 years of age (ZDHS, 2013) This age group is in the reproductive range and gets exposed to the risk factors of an ectopic pregnancy.

Most of the patients that presented at the hospital had attained secondary level education (51.1%) and the larger majority of the patients (62.2%) had household income in the range K500 – K2,000 which belongs to the lowest paid bracket. A larger majority of the women (81.1%) were married/cohabiting followed by those that were single/never married (15.6%).

The most common risk factor was ‘having more than 1 sexual partner ever’ (55.6%) and ‘multiple sexual partners at one time ever’ (14.4%). Ten percent had been treated for an STI. Multiple sexual partners predispose patients to acquiring sexually transmitted infections leading to pelvic inflammatory which, according to studies done in Africa, is a major risk factor for developing an ectopic pregnancy (Coste et al, 2003)

The most common symptoms at admission was lower abdominal or pelvic pain with (97.8%) of the patients presenting with the symptom, followed by amenorrhea with (83.3%). The least presenting symptoms were pain while having bowel movement and shoulder tip pain (12.2%) and (13.3%) respectively. The above findings agree with findings from other studies.

The most common site of ectopic pregnancy was the infundibulum (33.3%) and ampulla (28.8%). The ampulla is the widest part of the fallopian tube and the fertilization takes place here before the fertilized ovum migrates to a site of implantation. These findings are in keeping with several studies and literatures sources already quoted. In this study, there was no heterotopic pregnancy observed confirming that this is a rare condition.

Nearly all the patients underwent laparotomy (97.8%) patients. One patient (1.1%) was treated medically with methotrexate and folinic acid and in two cases the mode was not documented. No patient underwent laparoscopy for diagnosis or surgery.

Of those that had laparotomy, most had a salpingectomy as the tube could not be salvaged. The mode of treatment at UTH is laparotomy for all the patients with suspected or confirmed ectopic pregnancy. Patients usually presented late when to UTH and most of the patients did not fulfill the criteria for medical treatment which is non-viable fetus, gestation sac of less than 4cm, beta HCG of 1500 i.u. Follow up for these patients is a challenge as most of these are socially economically challenged with poor heath seeking behavior. As for laparoscopy, most of the patients did not fulfill the criteria as a haemodynamically stable patient is needed to undergo the procedure. There is lack of equipment and little expertise among obstetrician and gynecologists at the hospital to provide such an emergency service.

Haemoperitoneum was present in over three quarter of cases (77.8%). In addition, 70% had a ruptured ectopic. This shows that most patients presented late when the ectopic pregnancy had ruptured making it difficult to salvage or save the affected tubes and let alone effect other treatment modalities other than laparatomy.

As a result of the high proportion of ruptured ectopic pregnancy, the blood loss was high with 32.9% and 31.4% of cases having an estimated blood loss of between 500-

1000mls and >1000mls respectively. Blood transfusion was hence needed in just under half the cases (48.9%) and most received one or two units of blood (38.6% for both groups).

Whereas most the patients were admitted to the general wards (93.3%), a few (4/90, 4.4 %), all four with ruptured ectopic pregnancies, were admitted to a high dependency unit needing close monitoring as their conditions were critical after having lost a substantial amount of blood. The median duration from admission to discharge was 4 days with minimum 2 days and maximum 8 days. The patients that were discharged at 2 days were very stable and had mobilized on the first day with no intra and post-operative complications. The ones that stayed longer, up to eight (8 days) came in shock, had to be admitted to our high dependence ward and took time to receive blood before being discharged. It is noteworthy that in this series, the case fatality was only 1 in 90 (1.1%).

6. STUDY LIMITATIONS

The results of the study cannot be generalized as the findings are institutional specific to a tertiary hospital.

7. CONCLUSION

The incidence of ectopic pregnancies was 0.05% of all cases (early and late pregnant women) seen in the department with a case fatality rate of (1.1%). Patients presenting with lower abdominal pain, amenorrhea with a positive pregnancy test, the index of suspicion should be high for an ectopic pregnancy. The majority of patients presented late, with a ruptured ectopic pregnancy and had to undergo laparotomy, with ultimately a salpingectomy being done. Surgical treatment (laparotomy) is the current treatment executed for all ectopic pregnancies at UTH.

8. RECOMMENDATIONS

1. Early presentation, high index of suspicion and use of modern diagnostic techniques will improve overall clinical outcome in patients with ectopic pregnancies
2. Build capacity in doctors in the department in doing laparoscopic surgery
3. To implement other treatment options (medical and laparoscopic) for patients that came with ectopic pregnancies.

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10. APPENDICES

Appendix 1 - Participant information sheet and consent

A Study of an Epidemiology (Determinants, Distribution, and Frequency of Disease) on Ectopic Pregnancies at the University Teaching Hospital, Lusaka.

Principal Investigator: Dr. Sume Percival Chisha
Address: Department of Obstetrics and Gynecology, The University Teaching Hospital, P/B RWX 1, LUSAKA

Sponsor: GRZ

Dear Mrs./Ms.….,
I invite you to take part in this study about ectopic pregnancies by Dr. Sume Percival Chisha. The doctors think you have an ectopic pregnancy. An ectopic pregnancy is a pregnancy outside of the uterus.

The study is looking at the prevalence (frequency) of ectopic, common clinical presentations (physical signs and symptoms), and social demographic factors (socio-economic characteristics of a person) associated with ectopic pregnancies.

Study team members will ask you questions. They will also get information from your medical file.

This study will help us improve diagnosis and management of ectopic pregnancies. You will not get any money or material benefits in being part of the study. The study will not change the treatment of your condition.

Participants are free to withdraw from the study at any given time and not to answer questions they deem uncomfortable or sensitive.

If you agree to take part, please sign this consent form.

Consent Form

I understand all that has been explained to me as above. It is clear to me what this study is all about. I voluntarily consent to take part in the study. I agree to take part in the study on my own without coercion.

Name ---

Signature ---Date ------------------------------

Thumb print for illiterate patient ---------------

Name of witness, if illiterate --

Signature of witness, if illiterate -------------------------------------Date ------------------

Appendix 2 - Questionnaire for the participant

A Study of an Epidemiology (Determinants, Distribution, and Frequency of Disease) on Ectopic Pregnancies at the University Teaching Hospital, Lusaka.

Principal Investigator: Dr. Sume Percival Chisha
Address: Department of Obstetrics and Gynecology, The University Teaching Hospital, P/B RWX 1, LUSAKA

RISK FACTORS, SIGNS AND SYMPTOMS FOR AN ECTOPIC PREGNANCY

ID:_________________________ Date: _________________________

Address:_______________________

Please answer, tick or enter in the appropriate space.

1) Age of woman: ______ years old (Write 99 if unknown)

2) Education (highest completed)
   1. Less than primary
   2. Primary
   3. Secondary
   4. Tertiary
   5. Graduate
   6. Unknown

3) Monthly household income
   1. < 500.00 kwacha
   2. 500.00 - 2,000.00 kwacha
   3. 2,000.00 - 5,000.00 kwacha
   4. 5,000.00 - 15,000.00 kwacha
   5. > 15,000.00 kwacha
   6. Unknown

4) Marital status
   1. Single/never married
   2. Married/cohabiting
   3. Divorced/widowed
   4. Unknown

5) History of previous caesarean delivery
   1. Yes
   2. No
   3. Unknown

6) HIV status
    1. Yes
    2. No
    3. Unknown

7) Last HIV test date, estimate if needed (dd/mm/yyyy) __________ (Write 99 if unknown)

8) Gravidity _________ (Write 99 if unknown)
9) Parity ____________ (Write 99 if unknown)

10) LNMP, estimate if needed (dd/mm/yyyy) ___________________ (Write 99 if unknown)
11) Gestational age based on LNMP __________________ weeks (Write 99 if unknown)

12) Receiving antenatal care
    1. Yes
    2. No
    3. Unknown

13) Symptoms at admission
    i) Amenorrhea
        1. Yes
        2. No
        3. Unknown
    ii) Lower abdominal or pelvic pain
        1. Yes
        2. No
        3. Unknown
    iii) Back ache
        1. Yes
        2. No
        3. Unknown
    iv) Shoulder pain
        1. Yes
        2. No
        3. Unknown
    v) Vaginal bleeding
        1. Yes
        2. No
        3. Unknown
    vi) Pain while having a bowel movement
        1. Yes
        2. No
        3. Unknown

vii) Loss of consciousness

1. Yes
2. No
3. Unknown

viii) Dizziness

1. Yes
2. No
3. Unknown

14) Risk factors

i) Treated for STI ever

1. Yes
2. No
3. Unknown

ii) Treated for vaginal discharge ever

1. Yes
2. No
3. Unknown

iii) History of unsafe abortion ever

1. Yes
2. No
3. Unknown

iv) Multiple sexual partners currently

1. Yes
2. No
3. Unknown

v) Multiple sexual partners at one time ever

1. Yes
2. No
3. Unknown

vi) More than 1 sexual partner ever

1. Yes
2. No
3. Unknown

vii) Assisted conception (IVF, clomiphene) with this pregnancy

1. Yes
2. No
3. Unknown

viii) Intrauterine contraceptive device (IUCD) currently

1. Yes
2. No
3. Unknown

ix) Previous history of ectopic pregnancy
1. Yes
2. No
3. Unknown

x) History of tubal surgery
1. Yes
2. No
3. Unknown

15) Signs at admission

i) Temperature ________ (00 = not recorded)

ii) BP ________ (00 = not recorded)

iii) HR ________ (00 = not recorded)

iv) RR ________ (00 = not recorded)

v) Clinician judgment that patient is in shock
1. Yes
2. No
3. Unknown

vi) Abdominopelvic tenderness (palpation)
1. Yes
2. No
3. Unknown

vii) Vaginal bleeding
1. Yes
2. No
3. Unknown

viii) Please mark all sources of data used for signs at admission:
1. Examination done by __________________ (write in name and position)
2. Medical record or file
3. Unknown

16) Investigations at admission

i) Pregnancy test
1. Positive
2. Negative
3. Unknown

ii) Ultrasound
1. Yes
2. No
3. Unknown

iii) If yes, type of ultrasound?
1. Official by ultrasound technician
2. Bedside by doctor/clinician
3. Unknown

iv) If yes, was ectopic pregnancy diagnosed on ultrasound?

1. Yes
2. No
3. Unknown

v) If yes, was haemoperitoneum or blood in the pouch of Douglass reported on ultrasound?

1. Yes
2. No
3. Unknown

vi) Culdocentesis

1. Yes
2. No
3. Unknown

vii) If yes, result of culdocentesis?

1. Blood
2. No blood
3. Unknown

Appendix 3 - Medical file extraction

A Study of Epidemiology (Determinants, Distribution, and Frequency of Disease) on Ectopic Pregnancies at the University Teaching Hospital, Lusaka.

Principal Investigator: Dr. Sume Percival Chisha
Address: Department of Obstetrics and Gynecology, The University Teaching Hospital, P/B RWX 1, LUSAKA

MANAGEMENT AND OUTCOMES FOR AN ECTOPIC PREGNANCY

ID:________________________ Date: ________________________

Please answer, tick or enter in the appropriate space.

1) Date of admission (dd/mm/yyyy) __________________________ (00 = not recorded)
2) Date of discharge (dd/mm/yyyy) __________________________ (00 = not recorded)

3) Mode of treatment at admission/early hospital stay
   1. Conservative (observation only)
   2. Medical with Methotrexate
   3. Surgical via laparoscopy
   4. Surgical via laparotomy
   5. Unknown/Not recorded

4) Definitive mode of treatment of ectopic pregnancy
   1. Conservative (observation only)
   2. Medical with Methotrexate
   3. Surgical via laparoscopy
   4. Surgical via laparotomy
   5. Unknown/Not recorded

5) If surgery, what was the procedure?
   1. Salpingotomy
   2. Salpingectomy
   3. Other, specify ____
   4. Unknown/Not recorded

6) If surgery, what were intraoperative findings?
   1. Ruptured ectopic pregnancy
   2. Unruptured ectopic pregnancy
   3. Heterotopic pregnancy with ruptured ectopic pregnancy
   4. Heterotopic pregnancy with unruptured ectopic pregnancy
   5. Unknown/Not recorded

7) If surgery, was there haemoperitoneum?
   1. Yes
   2. No
   3. Unknown/Not recorded

8) If haemoperitoneum, how much? _______________________ ml

9) Were there signs of infection, e.g. intra-operative pus?
   1. Yes
   2. No
   3. Unknown/Not recorded

10) If surgery, were there adhesions? \
   1. Yes
   2. No
   3. Unknown/Not recorded

11) Site of ectopic
   1. Fimbria
   2. Ampulla
   3. Isthmus
   4. Cornua
   5. Interstitial (within the uterus)
   6. Cervix
   7. Ovary
   8. Abdomen
   9. Other, specify ____
   10. Unknown/Not recorded

12) Heterotopic pregnancy?
   1. Yes
   2. No
   3. Unknown/Not recorded

13) Signs at discharge (last set of vital signs in medical file)
   i) Temperature ________ (00 = not recorded)
   ii) BP ________ (00 = not recorded)
   iii) HR ________ (00 = not recorded)
   iv) RR ________ (00 = not recorded)

14) Date of last set of vital signs (dd/mm/yyyy) _________________ (00 = not recorded)

15) Admission to high dependency unit?
1. Yes, SOU
2. Yes, Annex
3. Yes, main ICU
4. No
5. Unknown

16) Blood transfusion given?
1. Yes, _____ units of _______________________________
2. No/not recorded

17) If BT, then when/where given?
1. Pre-operatively in C-ward
2. Pre-operatively in OT
3. During operation
4. Post-operatively
5. Unknown timing/location

18) Outcome

1..Alive

2..Died

Appendix 4 – Ethics approval

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Rhodes Park, Lusaka
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+260 955 155 634
Cell: +260 966 765 503
Email: eresconverge@yahoo.co.uk

I.R.B. No. 00005948
F.W.A. No. 00011697

13th May, 2014

Ref. No. 2014-Jan-011

The Principal Investigator
Dr. Sume Percival Chisha
The University Teaching Hospital
Dept. of Obstetrics and Gynaecology
P/Bag RW IX, LUSAKA.

Dear Dr. Chisha,

RE: AN EPIDEMIOLOGY OF ECTOPIC PREGNANCY.

Reference is made to your corrections dated 7th May, 2014. The IRB members resolved to approve this study and your participation as principal investigator for-a period of one year.

Review Type	Ordinary	Approval No. 2014-Jan-011
Approval and Expiry Date	Approval Date: 13th May, 2014	Expiry Date: 12th May, 2015
Protocol Version and Date	17th December,2013	12th May, 2015
Information Sheet, Consent Forms and Dates	• English.	12th May,2015
Consent form ID and Date	Version-Nil	12th May,2015
Recruitment Materials	Nil	12th May, 2015
Other Study Documents	Questionnaire, Medical File Extraction.	12th May, 2015
Number of participants approved for study	88	12th May,2015

Specific conditions will apply to this approval. As Principal Investigator it is your responsibility to ensure that the contents of this letter are adhered to. If these are not adhered to, the approval may be suspended. Should the study be suspended, study sponsors and other regulatory authorities will be informed.

Conditions of Approval

- No participant may be involved in any study procedure prior to the study approval or after the expiration date.
- All unanticipated or Serious Adverse Events (SAEs) must be reported to the IRB within 5 days.
- All protocol modifications must be IRB approved prior to implementation unless they are intended to reduce risk (but must still be reported for approval). Modifications will include any change of investigator/s or site address.
- All protocol deviations must be reported to the IRB within 5 working days.
- All recruitment materials must be approved by the IRB prior to being used.
- Principal investigators are responsible for initiating Continuing Review proceedings. Documents must be received by the IRB at least 30 days before the expiry date. This is for the purpose of facilitating the review process. Any documents received less than 30 days before expiry will be labelled "late submissions" and will incur a penalty.
- Every 6 (six) months a progress report form supplied by ERES IRB must be filled in and submitted to us.
- ERES Converge IRB does not "stamp" approval letters, consent forms or study documents unless requested for in writing. This is because the approval letter clearly indicates the documents approved by the IRB as well as other elements and conditions of approval.

Should you have any questions regarding anything indicated in this letter, please do not hesitate to get in touch with us at the above indicated address.

On behalf of ERES Converge IRB, we would like to wish you all the success as you carry out your study.

Yours faithfully,

ERES CONVERGE IRB

Dr. E. Munalula-Nkandu
BSc (Hons), MSc, MA Bioethics, PgD WEthics, PhD
CHAIRPERSON