

**ASSOCIATION BETWEEN PROGESTERONE ONLY  
EMERGENCY CONTRACEPTIVE PILL AND ECTOPIC  
PREGNANCY**

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2015

## **STUDENTS DECLARATION**

This proposal is my original work and has not been presented for course work in this or any other university.

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**DECLARATION AND APPROVAL FROM SUPERVISORS:**

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## **DEDICATION**

Mum, Mrs. Jane Wambui Maina, you have been the wind beneath my wings. This is for you.

## **LIST OF ABBREVIATIONS**

**EC-** Emergency Contraceptive

**ACOG-** American College of Obstetricians & Gynaecologists

**A/E-** Accident & Emergency

**COC-** Combined Oral Contraceptives

**GFA** – Ground Floor A (ward)

**GFB** –Ground Floor B (ward)

**ICEC-** International Consortium for Emergency Contraceptive

**ICU-** Intensive Care Unit

**KNH-** Kenyatta National Hospital

**KDHS-** Kenya Demographic Health Survey

**LNG** – Levonogesterol

**MDG-** Millennium Development Goals

**MOH** – Ministry Of Health

**NGO-** Non Governmental Organization

**PDT-** Pregnancy Diagnostic Test

**PID-** Pelvic Inflammatory Disease

**POEC-** Progesterone Only Emergency Contraceptive

**PSI-** Population Services International

**PSK-** Pharmaceutical Society of Kenya

**SHO** - Senior House Officer

**UoN-** University of Nairobi

**WHO-** World Health Organisation

## **OPERATIONAL DEFINITIONS**

**Ectopic pregnancy** - pregnancy occurring in the fallopian tube.

**Intrauterine pregnancy** - pregnancy implanted within the endometrial lining of the uterus.

**Emergency contraceptive** - form of contraception taken after an act of unprotected sexual contact with the aim of preventing a pregnancy.

**Progesterone only emergency contraceptive pill** - any levonegestrol containing brand of emergency contraceptive pill.

**Sub fertility**- prolonged time of unwanted non- conception for more than 6 menstrual cycles.

**Infertility**- prolonged time of unwanted non-conception for more than 12 menstrual cycles.

## **RISK FACTORS STUDIED**

1. Progesterone only emergency contraceptive pills
2. Sexually transmitted infections
3. Sexual debut
4. Infertility/ subfertility
5. Previous abdominal pelvic surgery



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## **ABSTRACT**

**Introduction:** Ectopic pregnancy remains a significant cause of morbidity and mortality in the developing world, with mortality being 10 times higher in developing world compared to the developed countries. Diagnosis in the resource constrained countries requires a high index of suspicion based on possible risk factors in the affected individual for early treatment to reduce mortality and morbidity associated with late diagnosis. Emergency contraceptive pills significantly lower the chances of an unwanted pregnancy following unprotected coitus in the mid cycle, and consequently reduce unsafe abortions. Awareness on correct use of the emergency pills remains poor. Several cases of tubal ectopic pregnancy following the use of emergency contraceptive pill use have been reported, with majority supposedly due to incorrect use of the pill. This forms the basis of this study.

**Objective:** To identify if use of emergency contraceptive pill predisposes to ectopic pregnancy and assess other risk factors for ectopic pregnancy.

**Study setting:** This study was conducted at the Kenyatta National Hospital in the acute gynaecology ward, antenatal wards and antenatal clinics.

**Methods:** This was a case-control study matched for age. Consecutive sampling was used. Women diagnosed with ectopic pregnancy were recruited as the cases (n= 120). Women with intrauterine pregnancy were recruited as matched controls at a ratio of 1:1. Data was analysed using SPSS software (version 18.0). Multivariate logistic regression analysis was performed to calculate the odds ratios (OR) and the corresponding 95% confidence intervals (CI).

**Results:** Of the 120 cases and 120 controls recruited, 27.5% of the cases and 2.5% of the controls had taken Levonogestrel emergency contraceptive (LNG-EC) pill during the menstrual cycle leading to the current pregnancy. Of the cases, 72.7% took the LNG-EC within 24hrs after coitus, while all the controls took the pill within 24-48 hrs. Only 18.2% of the cases knew their fertile days. Majority of the cases (78.8%) swallowed both pills at once, and most women amongst the cases (n=24) and all the controls (n=3) took the pill in the secretory phase of their cycle. The risk of ectopic pregnancy (EP) increased 12-fold in women who had used LNG-EC (OR=12.44, 95% CI 3.1-49.84) after adjusting for other confounders. EP was associated with early sexual debut (p= 0.039), history of subfertility/infertility (OR=6.87, 95% CI 2.14-22.03).

Unplanned pregnancies were significantly associated with EP ( $p = \leq 0.001$ ). Previous treatment for STIs increased the risk of EP 3-fold (OR=3.01, 95% CI 1.45-6.21).

**Conclusion:** Failed POEC increases the risk of ectopic pregnancy.

Early sexual debut, infertility/subfertility and previous STIs are significant risk factors for ectopic pregnancy.

**Recommendation:** POEC should be recognized as a risk factor for ectopic pregnancy and included in the client information leaflet in the drug packaging.

Client education at the point of sale using information, education and communication (IEC) materials and advice on when to seek medical attention.

## **CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW**

Ectopic pregnancy occurs when the blastocyst implants outside the endometrium of the uterus. >95% of ectopic pregnancies occur in the fallopian tube, while the remaining 5 % includes cervical, ovarian and primary abdominal pregnancies<sup>1</sup>. Tubal pregnancies occur in different locations in the tube, with the ampulla region being the commonest site, 55%, isthmus 25%, fimbria 17% and interstitial 2%<sup>1</sup>. Ectopic pregnancy is the leading cause of first trimester pregnancy related maternal mortality in the developed world accounting for 4-10% of all maternal deaths in the United States of America<sup>2</sup>. In the developing world and Kenya in particular, unsafe abortion due to unwanted pregnancy is the leading cause of first trimester maternal mortality<sup>3</sup>. Ectopic pregnancy complicates 1-2% of all pregnancies<sup>2</sup>. In Kenya at the largest referral hospital, Kenyatta National Hospital in the year 2002, a total of 5 patients were admitted every week<sup>4</sup>. Current hospital statistics show that about 10 cases are admitted weekly. This increase is in keeping with the increasing incidence reported in other countries. In the USA, the incidence has been increasing since the 1970's from 4.5/1000 to 19.7/1000<sup>1</sup>. In Sudan, an incidence of 1:48 deliveries<sup>5</sup> was reported whereas in Cameroon an incidence of 8550 per 100,000 women with pelvic inflammatory disease was reported, with a case fatality of 100-300/10,000<sup>6</sup>. In African developing countries, most hospital based studies have reported case fatality rates of 1-3%, 10 times higher than that reported in the developed countries<sup>7</sup>. Ectopic pregnancy (EP) also has significant implications on future fertility with only a third of patients reported to conceive after salpingectomy for ectopic pregnancy<sup>8,9</sup>. A study at KNH reported that 5.9% of the patients had suffered a repeat ectopic pregnancy<sup>4</sup>.

Tubal ectopic pregnancy arises when the fertilized egg fails to migrate to the uterus. In principle therefore, any condition that prevents or delays migration would predispose to an EP. Pelvic inflammatory disease (PID) leading to salpingitis is associated with ectopic pregnancy, with more than 50% of women diagnosed with tubal ectopic pregnancy reported to have had salpingitis<sup>1</sup>. At the Kenyatta National Hospital (KNH), Miyoro et al. demonstrated that 56.6 % of patients treated for ectopic pregnancy between 1991- 2000 had features suggestive of PID<sup>4</sup>. Fabio Parazzini et.al in an Italian study reported a six-fold higher risk of ectopic pregnancy in patients with a history of PID<sup>10</sup>.

Previous tubal damage from surgery, adhesions secondary to abdominal/pelvic surgery are also known risk factors for ectopic pregnancy<sup>1, 11</sup>. An Italian study reported an estimated relative risk of 2.1 for cases with a previous abdominal surgery<sup>10</sup>. Alteration in tubal motility due to certain contraceptive methods has been shown to predispose to EP<sup>11</sup>. The use of progesterone-only contraceptive pills has a slightly increased risk of ectopic pregnancy, with reports of up to 4-6% EP rates<sup>1, 11</sup>. A systematic review published by the American College of Obstetricians and Gynaecologists (ACOG) however did not demonstrate an increased risk among women who had used progesterone only emergency contraceptive pill reporting an ectopic pregnancy rate of 0.6%- 1.1%, which falls within the reported ectopic pregnancy rates of 0.8%- 2%<sup>12-15</sup>. Conception with an intrauterine device in situ is more often associated with an ectopic pregnancy compared to no Intrauterine Contraceptive Device (IUCD)<sup>11</sup>.

Emergency contraceptive (EC), also known as postcoital contraception prevents pregnancy after an unprotected or inadequately protected act of sexual intercourse. Women seeking EC are typically younger than 25 years, have never been pregnant and have used a form of contraceptive in the past<sup>16</sup>. The methods of emergency contraception available include: intrauterine Contraceptive Device (IUCD), combination Estrogen-Progesterone pills, progesterone only emergency contraceptive (POEC) pills and antiprogestins – progesterone receptor antagonists and selective progesterone receptor modulators. The combination estrogen- progesterone pill also referred to as the YUZPE method consists of 2 doses of 100mcg ethinyl estradiol and 500mcg of levonogestrol taken at 12 hr interval. The POEC pill, marketed as “PLAN B” in the United States of America consists of 750mcg of levonogestrol taken 12 hours apart. However the POEC pill taken as 1.5mg at once is as effective as the interval dose, and tends to promote adherence<sup>17</sup>.

POEC had been available in some countries since 1979, but only till 1994 did a randomized trial by WHO show that it's more efficacious compared to the YUZPE method. It prevents 85% of unwanted pregnancies versus 57% for the YUZPE method, with a failure rate of 1.1% versus 3.2% respectively<sup>19</sup>. Trussel et al. published a study of patients who had correctly used levonogestrol emergency pills correctly and reported a failure rate of 5.2%<sup>18</sup>. LNG-EC reduces the risk of pregnancy following a single act of coitus in mid-cycle from 8% to 1.1 %<sup>12</sup>.

To maximize efficacy, EC pills should be started as soon as possible following sexual intercourse. Earlier studies demonstrated that it's effective if started within 72 hours after intercourse<sup>19,20</sup>. As a result, the product packaging advises that the EC pill is used within this time frame. More recent studies have however shown that the pill is effective taken upto 5 days (120 hours) after intercourse<sup>18,21-24</sup>. The Kenya National guidelines for family planning providers have since been modified allowing emergency contraception to be provided upto 120hrs<sup>25</sup>

In Kenya, Postinor a brand of POEC was registered and distributed in the private sector since 1992, however, postinor 2 was approved for use in the public sector by the Ministry Of Health (MOH) in 1997 following efforts by the International Consortium for Emergency Contraceptives (ICEC) and the local distributor. Kenya was among the first African countries to introduce EC in the public market. Following this introduction into the public market, use of EC remained low. By 2003, 24% of the women had heard about EC and 0.9% had used it<sup>28</sup>. Due to the low EC uptake, Population Council and Population services International (PSI), key members of the ICEC launched an initiative to support the MOH in creating awareness and providing EC at the national level, at the same time supporting private sector in its provision and allaying the public fears associated with increased access<sup>27</sup>. The media campaign which began in 2008 and lasted one year was undertaken and was preceded by a baseline survey and succeeded by an endline survey. A baseline assessment of knowledge, attitudes and practices in 2007 demonstrated that less than 50% of service providers and 10% of clients had heard about EC<sup>26,27</sup>. Among other indicators surveyed, 88% of women stated that the EC pills should be taken within 72hrs of unprotected coitus at baseline. By 2009, 56% of women had heard about EC and 10% had used it. 44% of eligible women were still not aware that EC exists by the end of the campaign, indicating the need for continued education and awareness.

Michieka Paul et al. in 2010 studied knowledge attitude and use of emergency contraceptives among adolescent girls in secondary schools in Nairobi and found out that of the 280 girls sampled, 57% knew about EC, with 81% having heard about it from their peers and 66.9 % from magazines and newspaper<sup>29</sup>. Of those who had heard about EC, 18% knew the correct timing and dosage of EC pills. From the study 8% (22) of the girls had engaged in sexual activity, and 73% of them used a form of contraception, out of which 50% (11) used EC. However the use of EC was not significantly associated with accurate information (P=0.16).



Pharmacy was the main source of the EC pill with 9 out of 11 having obtained the drug over the counter. A similar study among undergraduate female students at the Kenyatta University demonstrated that a majority of women knew about their fertile days and were contraceptive experienced. However despite the students being aware of existence of EC, mainly postinor -2, their knowledge on the timing and dosage for effective use of the method was low<sup>30</sup>.

The mechanism of action of POEC is multifactorial, no single mechanism has been established, and largely depends on the day of the cycle the pill is administered. Croxatto et al.<sup>31</sup> and Hapangama et al.<sup>32</sup> demonstrated that LNG administered just before ovulation in the follicular phase delays ovulation by upto 5 days and therefore explains why it is possible to conceive in the same cycle after the use of LNG if there is a second act of unprotected within the 5 days. A study done in rats demonstrated a 100% inhibition of ovulation when LNG was administered prior to follicular rupture in a dose dependent manner<sup>33</sup>. The study also demonstrated that LNG had no post fertilization effect. Other postulated mechanisms of action include interference with fertilization by decreasing the tubal motility and inhibition of implantation in the post ovulatory period<sup>34</sup>. Pulkinen and Talo described the physiology of tubal ciliary and myoelectrical activity, and reported that estrogens stimulate tubal myoelectrical activity while progesterone's inhibit it, which could lead to a delay in transport of the fertilized ovum to the uterus<sup>35,36</sup>. Alteration in the capacity of sperms and changes in the cervical mucus consistency which prevent sperm motility into the cervical canal are also common effects of LNG pills<sup>19,24,34,37</sup>. Use of LNG-EC within 10hrs after coitus was shown to reduce the number of spermatozoa recovered from uterine cavity of users<sup>37</sup>. Other studies suggest histological and biochemical changes in the endometrium which alters the receptiveness of the endometrium for implantation<sup>34</sup>. Several recent studies have however disputed the endometrial theory<sup>33</sup>.

There are concerns of ectopic pregnancy following the use of LNG-EC<sup>38-42</sup>. The most effective period of LNG pill use has been reported to be in the pre-ovulatory follicular phase<sup>34,35</sup>. Use after the ovulatory period and increased interval between unprotected intercourse and start of treatment have been described as the main causes of failure<sup>38</sup>. Farkas et al. reported an ectopic pregnancy rate of 6.4% among patients who had used LNG pills<sup>42</sup>.

Concerns of ectopic pregnancy following failure of POEC was first raised by the New Zealand Medicines and Medical Safety Authority (NZMMSA) in 2003, where several cases of ectopic pregnancies were reported in patients following correct use of levonogestrol emergency pills and some who seemingly did not have any other risk factors for ectopic pregnancy<sup>43</sup>. Following the observation by NZMMSA, the Britain's Committee on Safety of medicines advised that if a woman who had used POEC pill has delayed menses or has a positive pregnancy test then "the possibility an ectopic pregnancy should be considered"<sup>44</sup>. Several other cases have been reported and published. Pedro Paulo Pereira et.al presented 2 cases of patients with no other identifiable risk factors who had taken LNG emergency pills who presented with ectopic pregnancy and warned that special attention should be paid to patients who use POEC pills and present with lower abdominal pains or genital bleeding in anticipation for ectopic pregnancy and therefore improve outcome<sup>38</sup>.

Several case reports have been published of women who took the POEC with seemingly no other risk factors and ended up with an ectopic pregnancy<sup>41,43,45,47,48</sup>. They all recommended that an EP should be considered if menses are delayed after use of POEC.

In response an article by Jane Wooley et. al on several case reports<sup>43</sup>, Erin, Christian and Ulmann all working for the French Pharmaceutical company that holds market authorization for a progesterone only emergency contraceptive pill noted that in their post market study 20 months after POEC was availed in France, only 3 cases of ectopic pregnancies had been reported out of the 2500 prescriptions that had been issued. Four years later only 8 cases had been reported in France and therefore concluded that emergency contraceptive pill is effective in preventing ectopic pregnancy in general, and that treatment failure rates do not exceed those of the general population<sup>46</sup>.

Kelly Cleland, Elizabeth et al. in a systematic review of 137 studies of Mifepristone and Levonogestrol emergency contraceptive pills concluded that the ectopic pregnancy rates among women with failure of hormonal emergency contraceptives does not exceed the rates in the general population. They calculated ectopic pregnancy rates of 0.8% for Mifepristone and 1.6 % for levonogestrol<sup>12</sup>. This falls within the incidence rates in the general population of 1- 2 %<sup>2</sup>. The review provides the most comprehensive assessment to date of the risk of ectopic pregnancy following hormonal emergency contraceptive failure.

A study done in Hong Kong between 2006-2008 describing characteristics of women seeking EC reported a failure rate of 1.8% following LNG-EC which is higher than the 1.1% reported by WHO and found an ectopic pregnancy rate of 2.3%, slightly higher than that of the general population<sup>49</sup>.

Gainer et.al. reported an ectopic pregnancy rate of 4.1% following failure of LNG-EC<sup>50</sup>.

A multicentre case- control study conducted recently in china between 2011- 2013 reported a four-fold higher risk of EP following failure of LNG-EC in the index cycle<sup>51</sup>.

## **STUDY JUSTIFICATION**

Kenyatta National hospital is the largest referral hospital in the country and therefore receives a large percentage of referrals from all over the country and from surrounding facilities in Nairobi. There is no recent data on ectopic pregnancy, the last study having been conducted more than 10 years ago. Ectopic pregnancy remains one of the leading causes of morbidity and mortality from attendant complications. Future fertility following an ectopic pregnancy remains low and the risk of a repeat ectopic pregnancy significant, therefore its crucial to educate patients on the risk factors for ectopic pregnancy and signs of a possible ectopic for early intervention. Most of the documented cases of ectopic pregnancy in relation to emergency contraceptive pills are based on case reports.

## **NULL HYPOTHESIS:**

Exposure to hormonal emergency contraceptive pill does not increase the risk of ectopic pregnancy

## **RESEARCH QUESTION**

Is there an association between women with confirmed ectopic pregnancy and recent use of emergency contraceptive pill

## **OBJECTIVES**

### **Broad objective:**

To determine the association between use of hormonal emergency contraceptive pill and ectopic pregnancy

### **Specific objectives:**

1. To determine the difference in the use, dosing, timing, dose compliance and frequency of emergency contraceptive pill use between women diagnosed with ectopic pregnancy and those with intrauterine pregnancy.
2. To describe the difference in sexual debut, previous sexually transmitted infection, history of infertility/subfertility and previous abdominal pelvic surgery between patients with ectopic pregnancy and those with intrauterine pregnancy.
3. To determine if use of emergency contraceptive pill is significantly associated with ectopic pregnancy.

## **CHAPTER TWO**

### **MATERIALS AND METHODS**

#### **Study design:**

This was a case control study, matched for age, the cases being patients with a diagnosis of ectopic pregnancy and the controls being women with an intrauterine pregnancy irrespective of the gestational age. Exposure to the emergency pill and other risk factors for ectopic pregnancy was compared between the two groups. Enrollment of patients was carried out in acute Gynaecology ward 1D, antenatal clinics and antenatal wards

#### **Study site and setting:**

Kenyatta National Hospital is located in Upper Hill, Nairobi, the capital of Kenya, Nairobi County. It is the major referral hospital for the whole country with a bed capacity of 2500 patients. It is the largest hospital in East and Central Africa and serves as the teaching hospital for the University of Nairobi School (UON) of Medicine and the Kenya Medical Training College (KMTC).

The gynaecology emergency and outpatient room (room 7) is located in the Accident and Emergency (A/E) department at KNH. It is run by a Senior House Officer (SHO) enrolled in postgraduate training at the UON on a 24 hour basis. All obstetrics and gynaecological emergencies are reviewed in this room and stabilized. They are then admitted to the antenatal/postnatal wards, acute gynaecological ward, Intensive Care Unit (ICU), discharged home or referred to the specialist clinics. All patients diagnosed with ectopic pregnancy are prepared for emergency theatre in the gynaecological A/E room and wheeled to theatre from where they are then transferred to the acute gynaecology ward 1D or to the ICU if need be.

The acute gynaecology ward is staffed by a SHO, medical officer interns and clinical officer interns on a 24 hr basis. Patients are reviewed daily by the consultant gynaecologist during the morning ward round. All post operative ectopic pregnancy patients not requiring ICU care are admitted to this ward.

Antenatal care services are offered at the ANC clinics that run daily from (booking clinic on Mondays) to Thursday. These clinics are run by a team of Consultants, SHO's and highly trained Nursing Officers. Antenatal mothers requiring inpatient care are admitted to the antenatal ward GFA, GFB and ward 1A.

The study cases were patients diagnosed as having an ectopic pregnancy.

The controls were patients with an intrauterine pregnancy irrespective of gestational age

Recruitment was done post operatively in the acute gynaecological ward 1D for the cases, antenatal clinic 18 and antenatal wards GFA, 1A, GFB for the controls.

### **Inclusion criteria:**

#### **Cases:**

Women  $\geq 18$  years who were:

- Admitted with a diagnosis of ectopic pregnancy who consented to the study.

#### **controls**

- Pregnant Women visiting clinic 18 for antenatal care who consented to the study.
- Pregnant Women admitted in the antenatal wards who consented to the study.

### **Exclusion criteria:**

- Women who had had a previous ectopic pregnancy.
- Very sick patients requiring ICU / Renal Replacement therapy.
- Patients operated elsewhere and referred to KNH due to complications of ectopic pregnancy.
- Antenatal mothers who were very sick.

### **Sample size calculation:**

The following assumptions were used in calculating sample size using the formula for case-control study design:

$$n = \left(\frac{r + 1}{r}\right) \frac{(\bar{p})(1 - \bar{p})(Z_{\beta} + Z_{\alpha/2})^2}{(p_1 - p_2)}$$

- For 80% power,  $Z_{\beta}=0.84$
- For 0.05 significance level,  $Z_{\alpha}=1.96$
- $r=1$  (equal number of cases and controls)
- $p_1$ =The proportion exposed to emergency pills in the control group is 10%
- $p_2$ =Proportion of cases exposed to emergency pills is 25%
- $\bar{p}$  = average of  $p_1$  and  $p_2$

$$n = \left(\frac{1+1}{1}\right) \frac{(0.175)(1-0.175)(0.84+1.96)^2}{(0.1-0.25)^2} = 113$$

**Therefore, n = 226 (113 cases, 113 controls)**

However, the principal investigator interviewed a total of 120 participants on each arm. This was done with the intention of increasing the power of the study.

### **Recruitment and consenting procedure:**

Two research assistants were trained by the principal investigator once ethical approval was granted.

Consecutive sampling was used. The first 120 patients in each arm were recruited by either the principal investigator or the research assistants.

The cases were recruited in the acute gynaecological ward 1D post operatively.



Files of patients admitted with a diagnosis of ectopic pregnancy as per the admission register were retrieved. A diagnosis of tubal ectopic pregnancy was confirmed from the intraoperative notes and the patients with a tubal pregnancy were recruited into the study.

The controls were recruited from either the antenatal clinics or the antenatal wards. Those who had an ultrasound confirming an intrauterine gestation at any point in the index pregnancy were recruited into the study.

The study was explained to all the participants and thereafter an informed consent was obtained from the eligible participants. See appendix 1 for informed consent.

A questionnaire was then administered by the principal investigator / research assistant.

### **Diagnostic criteria:**

Ectopic pregnancy is one of the commonest gynaecological emergencies presenting in the Accident and Emergency department. Diagnosis is largely clinical depending on the clinical presentation of a period of amenorrhea, lower abdominal pain more on one side, +/- vaginal bleeding. Examination findings will usually reveal a tender adnexal mass. If the ectopic has ruptured, patients will be hypotensive with a tachycardia, a degree of pallor that is greater than the amount of bleeding and a positive paracentesis with non clotting blood. Patients admitted with suspicion of an ectopic pregnancy are immediately taken to the operating theatres from the Accident and Emergency department before being transferred to the acute gynaecology ward 1D post-operatively

Diagnosis of ectopic pregnancy largely depends on clinical presentation of patients at the emergency department.

Haemodynamically stable patients admitted with clinical suspicion of ectopic pregnancy underwent a pregnancy test and a pelvic ultrasound to confirm the diagnosis as is routinely done in the A/E department without any extra charges.

Haemodynamically compromised patients were diagnosed based on clinical assessments of a patient presenting with a period of amenorrhea and corroborated with intraoperative finding.

## **DATA COLLECTION:**

After obtaining ethical approval from ERC, permission was granted by the head of KNH Reproductive Health department to the principal investigator and the research assistants to access patients and their files.

## **DATA ANALYSIS AND PRESENTATION:**

Data was analyzed using SPSS software (version 18.0). Descriptive univariate statistics was calculated to summarize socio-demographic characteristics of women with confirmed tubal ectopic pregnancy and women with intrauterine pregnancy. Continuous variables including age were summarized using mean and standard deviation. For continuous variables showing evidence of skewed distribution median, range and interquartile range were calculated. Categorical factors e.g. frequency of emergency pill use, dose compliance and dosing were summarized using univariate frequency distribution tables showing frequencies and percentage of women in each category. Bivariate analysis was then used to identify risk factors associated with tubal pregnancy and those factors associated with intrauterine pregnancy. The categorical risk factors including emergency contraceptive use were cross tabulated with type of pregnancy (tubal or intrauterine) and comparisons were done using the chi-square or Fisher's exact test, as appropriate. Students T-test was used to compare means of continuous variables in the group with confirmed tubal or intrauterine pregnancy. Finally, logistic regression was used to conduct multivariable analysis with the binary variable for tubal or intrauterine pregnancy as the outcome (dependent variable) and the risk factors showing significant associations with tubal pregnancy as the independent variables. Statistical significance was based on an alpha level of 0.05. See dummy tables appendix II

## **ETHICAL CONSIDERATION:**

The study proposal was approved by the Department of Obstetrics and Gynaecology before submission to ethics committee. Ethical approval from the Ethics and Research Committee of KNH /UON was granted for this study. Permission to conduct the study was granted by the KNH Head of Department Reproductive Health, KNH Reproductive Health Research Coordinator and KNH Research and Programmes Coordinator .

Informed consent was obtained from the patients. All the information obtained from the patients was strictly used for purposes of this study and no identifying data was collected from the patients. The principal researcher and the research assistant maintained strict confidentiality at all times.

Appropriate health education was provided to the participants, and those who required counseling following the loss of a pregnancy were referred to the Patient Support Centre, KNH.

## **LIMITATIONS:**

### **Cases:**

The main limitation of this study was recall on when the emergency pill was taken in regard to their menstrual cycle. Majority of the participants however were noted to have recorded the dates of their last menstrual period and the dates they had unprotected coitus on their phone calendars.

### **Controls:**

The main limitation among the controls was lack of an obstetric ultrasound hence could not be recruited into the study.

## **CHAPTER THREE**

### **RESULTS**

During the study period, a total of 120 women with an index ectopic pregnancy at KNH were recruited into the study. Each of the 120 cases of ectopic pregnancies was matched for age to a control with intrauterine pregnancy (n = 120). Adequate age matching was achieved with an average age of 26.9 years (SD 6.2) among cases compared to an average age of 26.7 (SD 6.2) among controls. The most frequent age groups were 25-29 years.

**Table 1: Demographic characteristics of ectopic pregnancy cases compare to controls**

	Cases	Control	OR(95% CI)	P value
<b>Age in years</b>				
<19 years	5(4.2)	5(4.2)	1.00	
20-24 years	30(25.0)	30(25.2)	1.00(0.26-3.81)	1.000
25-29 years	43(35.8)	42(35.3)	1.02(0.28-3.80)	0.972
30-34 years	31(25.8)	31(26.1)	1.00(0.26-3.80)	1.000
>=35 years	11(9.2)	11(9.2)	1.00(0.22-4.46)	1.000
<b>Level of formal education</b>				
Primary	28(23.3)	18(15.1)	1.00	
Secondary	43(35.8)	45(37.8)	0.61(0.30-1.27)	0.188
Tertiary	21(63.6)	1(33.3)	0.55(0.27-1.12)	0.098
<b>Marital status</b>				
Married	71(59.2)	98(82.4)	1.00	
Single	39(32.5)	13(10.9)	4.14(2.06-8.32)	<0.001
Separated	10(8.3)	8(6.7)	1.72(0.65-4.59)	0.275

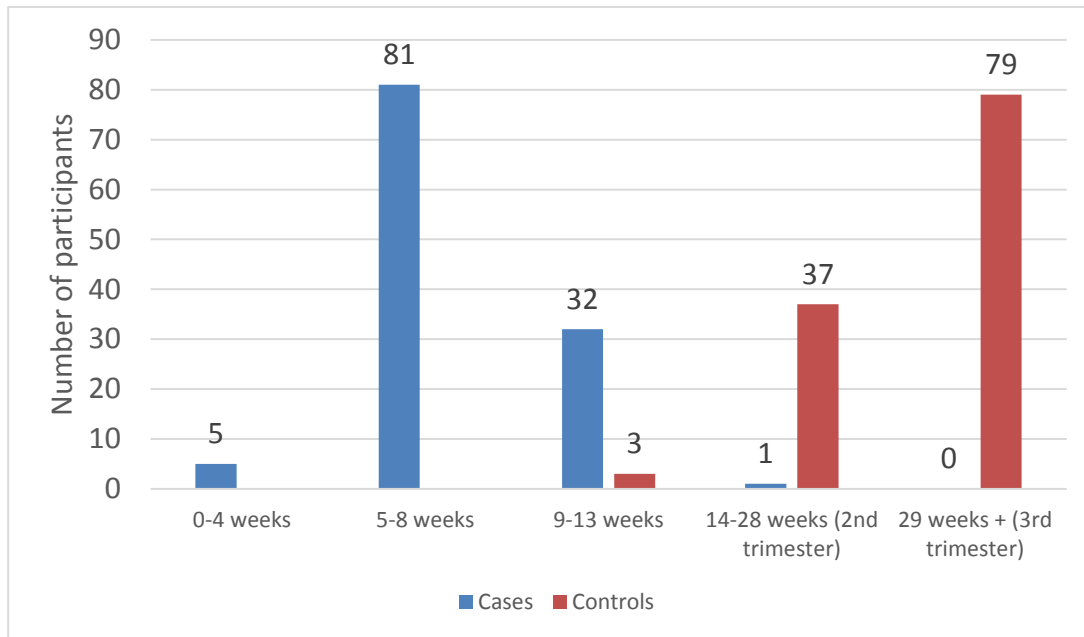
**Table 1:** The risk of ectopic pregnancy was higher in single women. The single women were approximately four times more likely to have an ectopic compared to married women (OR = 4.14, 95% CI 2.06-8.32,  $p < 0.001$ ).

## Obstetric and gynecologic history

Forty-four (36.7%) cases reported that the index pregnancy was planned and 72 (60.5%) controls similarly reported that the pregnancy was planned. Among these group of planned pregnancies 41 (93.2%) cases and 63 (87.5%) controls indicated that the pregnancies were timely.

Figure 1 presents gestational age of pregnancies according to case-control status. The modal gestational age among cases with ectopic pregnancies was 5-8 weeks, 81 (67.5%, 95% CI 58.3% - 75.8%) while among controls with intrauterine pregnancy the modal gestation age was 29-42 weeks, 79 (65.8%, 95% CI 56.6% - 74.2%).

Fig 1: gestational age of cases and controls



**Table 2: Parity: Cases as compared to Controls**

	<b>Cases</b>	<b>Control</b>	<b>OR (95% CI)</b>	<b>p value</b>
<b>Parity</b>				
0	41(34.2)	57(47.9)	1.00	
1 to 2	70(58.3)	53(44.5)	1.84(1.07-3.14)	0.027
3 to 4	7(5.8)	6(5.0)	1.62(0.51-5.18)	0.415
$\geq 5$	1(0.8)	2(1.7)	0.70(0.06-7.93)	0.77

There was a significant association between parity and ectopic pregnancy with women of parity between 1 and 2 having a higher risk of ectopic (OR = 1.84, 95% CI 1.07-3.14, p = 0.027) compared to prim gravid women.



## EMERGENCY CONTRACEPTIVE PILL USE

**Table 3: Emergency contraceptive pill use among cases of ectopic pregnancy and controls**

	Cases	Control	OR (95% CI)	p value
<b>Used emergency pill in the index menstrual cycle</b>				
Yes	33(27.5)	3(2.5)	14.71(4.37-49.55)	<0.001
No	86(71.7)	115(96.6)	1.00	
<b>Timing of emergency pill use(n = 36)</b>				
< 24 hours	24(72.7)	0(0.0)	NA	NA
24-48 hours	7(21.2)	3(100.0)	NA	
48-72 hours	2(6.1)	0(0.0)	NA	
<b>Do you know your fertile days?</b>				<b>0.34</b>
Yes	11(9.2)	7(5.9)	1.00	
No	109(90.8)	112(94.1)	0.62(0.23-1.66)	
<b>Frequency of emergency pill use in one month preceding index pregnancy</b>				
Never used	101(84.2)	111(93.3)	1.00	
Once	14(11.7)	6(5.0)	2.56(0.95-6.93)	0.063
Twice	3(2.5)	1(0.8)	3.30(0.34-32.21)	0.305
Three or more times	2(1.7)	1(0.8)	2.20(0.20-24.61)	0.523

**Table 3.** The risk of an ectopic pregnancy was 14 times higher in women reporting use of the emergency pill in the index menstrual cycle compared to women who did not use emergency pill during the period (OR = 14.71, 95% CI 4.37 – 49.55,  $p < 0.001$ ).

Among controls, all three women who took the pill, reported using it between 24 and 48 hours of coitus, while majority (72.7%) of the cases used the pill within 24 hours of coitus. Frequency of emergency pill use in the one month preceding the pregnancy was not associated with the risk of ectopic pregnancy (Table 3).

The  $p$  values accompanying the Odds Ratio and 95% confidence intervals were derived from logistic regression models. The  $P$  values were also calculated using Chi square test and for small samples Fischers exact tests were applied.

**Table 4: Demographic and obstetric characteristics of emergency pill users**

	<b>Cases</b>	<b>Control</b>	<b>P value (Fisher's exact)</b>
<b>Age in years</b>			
<19 years	2(6.1)	1(33.3)	0.185
20-24 years	14(42.4)	0(0.0)	
25-29 years	8(24.2)	1(33.3)	
30-34 years	7(21.2)	1(33.3)	
>=35 years	2(6.1)		
<b>Level of formal education</b>			
Primary	3(9.1)	0(0.0)	0.428
Secondary	9(27.3)	2(66.7)	
Tertiary	21(63.7)	1(33.3)	
<b>Parity</b>			
0	17(51.5)	1(33.3)	0.300
1 to 2	14(42.4)	1(33.3)	
3 to 4	1(3.0)	1(33.3)	
5	1(3.0)	0(0.0)	

The characteristics of emergency pill users are presented in Table 4. In the ectopic pregnancy group 42.4% of emergency pill users were aged between 20 and 24 years while among the three users with intrauterine pregnancies a single participant was found in each of the following age groups: <19, 25-29 and 30-34 years. Forty five percent of the cases who used emergency pills had college level education while 2 out of the 3 controls using emergency pills had secondary level education.

**Table 5: Knowledge and administration of oral emergency contraceptive in emergency pill users**

	Cases	Control	P value (Fisher's exact)
<b>Knowledge of fertile days</b>			
Yes	6(18.2)	1(33.3)	0.488
No	27(81.8)	2(66.7)	
<b>Emergency pills swallowed</b>			
Both at once	26(78.8)	3(100.0)	1.000
Swallowed at Interval	7(21.2)	0(0.0)	
<b>Given instruction on how to take drugs</b>			
Yes	11(33.3)	3(100.0)	0.051
No	22(66.7)	0(0.0)	
<b>Emergency pill use in preceding month</b>			
Not used	22(66.7)	2(66.7)	1.000
Used at least once	11(33.3)	1(33.3)	
<b>Phase of cycle during which pill was taken</b>			
Follicular	4(12.1)	1(33.3)	0.603
Ovulatory	4(12.1)	0(0.0)	
Secretory	24(72.7)	2(66.7)	
<b>Duration between coitus and taking pill</b>			
< 24 hours	24(72.7)	0(0.0)	0.034
24-48 hrs	7(21.2)	3(100.0)	
48-72 hrs	2(6.1)	0(0.0)	

**Table 5:** shows level of knowledge of emergency pill users according to case-control status. Six (18.2%) cases and 1 (33.3%) control knew the fertile days; 33.3% and all three controls were given instructions on how to take pills and 78.8% of cases and all three controls swallowed both pills at once. Two thirds of cases (66.7%) and two of the controls reported having taken emergency pills in the preceding month. Twenty four (72.7%) controls took the pill within 24 hours of coitus and the three controls took the pill between 24 and 48 hours after coitus. Most women in both groups (n = 24 cases, n = 3 controls) took the emergency pill during the secretory phase of the menstrual cycle. All the study participants who took the emergency pill (n=33 cases, n= 3 controls) obtained the pill from a chemist.

**Table 6: Other risk factors associated with ectopic pregnancy**

	Cases	Control	OR (95% CI)	p value
<b>Age at sexual debut</b>				
<15 years	9(7.5)	2(1.7)	7.87(1.10-56.12)	0.039
16-19 years	69(57.5)	60(50.4)	2.01(0.56-7.21)	0.283
20-24 years	38(31.7)	50(42.0)	1.33(0.36-4.87)	0.667
>=25 years	4(3.3)	7(5.9)	1.00	
<b>History of inability to conceive (&gt; 6 months after discontinuing contraceptive)</b>				
No	94(78.3)	112(94.1)	1.00	
Yes	21(17.5)	5(4.2)	5.00(1.82-13.78)	0.002
<b>Long-term contraception (1 year prior to conception)</b>				
None	82(68.3)	80(67.2)	1.00	
Pills	20(16.7)	13(10.9)	1.50(0.70-3.22)	0.297
IUCD	3(2.5)	4(3.4)	0.73(0.16-3.37)	0.689
Implant	3(2.5)	7(5.9)	0.42(0.10-1.67)	0.218
Injectable	12(10.0)	14(11.8)	0.84(0.36-1.92)	0.673
<b>Timely pregnancy</b>				
Yes	41(34.2)	63(52.9)	1.00	
No	79(65.8)	56(47.1)	2.17(1.29-3.65)	0.004

Other risk factors for ectopic pregnancy not related to emergency pill use were analyzed and are presented in Table 6. Among these risk factors, the ectopic pregnancy was significantly associated with: early sexual debut ( $p = 0.039$ ), history of inability to conceive immediately after discontinuing contraception ( $p = 0.002$ ), unplanned ( $p < 0.001$ ) and untimely pregnancies ( $p = 0.004$ ). The risk of ectopic increased 7 times in women reporting sexual debut before 15 years of age compared to debut after 25 years (OR = 7.87, 95% CI 1.10-56.12). Prior history of inability to conceive before the index pregnancy increased the risk of ectopic pregnancy 5 times (OR = 5.0, 95% CI 1.82-13.87).

**Table 7: Reproductive health treatment interventions in ectopic pregnancy cases and controls**

	Cases	Control	OR (95% CI)	p value
<b>History of pelvic surgery</b>				
Yes	20(16.7)	27(22.7)	1.00	
No	100(83.3)	92(77.3)	1.47(0.77-2.79)	0.243
<b>Previous treatment for STI</b>				
Yes	30(25.0)	12(10.1)	3.01(1.45-6.21)	0.003
No	89(74.2)	107(89.9)	1.00	
<b>History of tuboplasty</b>				
Yes	4(3.3)	2(1.7)	1.00	
No	116(96.7)	116(97.5)	0.50(0.09-2.78)	0.429

The impact of various reproductive health treatment interventions on the risk of ectopic pregnancy are presented in Table 7. Previous STI treatment was significantly associated with ectopic pregnancy risk ( $p = 0.003$ ), but history of pelvic surgery ( $p = 0.243$ ) and tuboplasty ( $p = 0.429$ ) were not associated with ectopic pregnancy. The risk of an ectopic pregnancy increased three fold in women who had previously received STI treatment (OR = 3.01, 95% CI 1.45-6.21).

**Table 8: Adjusted odds ratio of the risk of ectopic pregnancy from logistic regression**

	Odds			
	Ratio	p value	95% CI	
<b>Marital status</b>				
Married	1.00			
Single	4.53	0.004	1.62	12.62
Other	0.76	0.676	0.20	2.80
<b>Level of education</b>				
Primary	1.00			
Secondary	0.44	0.09	0.17	1.14
College	0.41	0.089	0.15	1.15
University	1.05	0.942	0.28	4.01
<b>Parity</b>				
Primigravid	1.00			
Para 1-2	3.85	0.001	1.71	8.67
Para 3-4	1.99	0.363	0.45	8.83
Para 5 and above	0.23	0.474	0.00	13.15
<b>Risk factors associated with EP</b>				
History of use of emergency pill in index pregnancy	12.44	<0.001	3.10	49.87
Age at sexual debut	0.66	0.124	0.39	1.12
Unplanned pregnancy	1.61	0.539	0.35	7.40
Untimely pregnancy	0.95	0.944	0.21	4.30
Inability to conceive	6.87	0.001	2.14	22.03
Previous STI treatment	3.09	0.013	1.27	7.48



Multivariable regression analysis was conducted using a logistic regression model to determine the independent predictors of the risk of ectopic pregnancy. The results of the regression analysis are presented in Table 8

The independent predictors of ectopic pregnancy were: history of emergency pill use in index pregnancy ( $p < 0.001$ ), inability to conceive after discontinuing contraception ( $p = 0.001$ ), and previous STI treatment ( $p = 0.013$ ). After adjusting for the confounding effect of marital status, education level, parity, age at sexual debut and planning for index pregnancy, the risk of ectopic pregnancy increased 12-fold in women who had used emergency contraception (OR = 12.44, 95% CI 3.10 – 49.87). The risk of ectopic pregnancy also increase 3 times and 6 times, in women with history of STI treatment (OR = 3.09, 95% CI 1.27-7.48) and inability to conceive (OR = 6.87, 2.14-22.03), respectively.

## **DISCUSSION**

The objective of this study was to find out if use of emergency contraceptive pills increases the risk of ectopic pregnancy. A significant association was noted from the study, with 27.5% of patients with EP reporting to have taken LNG-EC in the index menstrual cycle compared to 2.5% of the controls, which gave a twelve-fold increase in the risk of EP if LNG-EC fails. This increase though higher is in keeping with a recently published multicenter case control study done in China between 2011 and 2013 which reported a three-fold increase in EP after failure of EC (51). Farkas et al. in their study *the effect of oral ovulation inhibitor contraceptives and postinor on steroid hormones* reported an ectopic pregnancy rate of 6.4% following failure of LNG-EC(42). A systematic review by Cleland et al. however showed no increase in the risk of EP after use of LNG-EC, reporting that the rates of ectopic pregnancy was 0.8% , which falls within the general population rates of 1-2% (2). Most of the studies used in the systematic review however did not use EP as their end point. Two epidemiological studies reported higher rates of EP following failure of LNG-EC. In Hong Kong in 2008, a failure rate of 1.8% with an ectopic pregnancy rate of 2.8% was reported (49), and Gainer et al. reported an ectopic pregnancy rate of 4.1% after failure of LNG- EC(50).

There was no statistically significant between ectopic pregnancy and level of education from this study. The recent study done in China however found that EP occurred more often in women with lower level education compared to those with tertiary education (51). A study done in Italy did not show any association between education level and the occurrence of EP (10).

Single women were four times more likely to have an EP compared to married women. This is most likely due to the possibility of high risk sexual behavior and multiple sexual partners among the single women. Miyoro found no statistical significance with marital status (4).

The study in China similarly did not show any statistical significance between marital status and the risk of EP(51).

There was a significant association between parity and EP, with women para 1-2 being at a higher risk of EP compared to nulliparous women. From this study 92.5% of all cases had a parity of  $\leq 2$ , with 34% being nulliparous. This is in keeping with other studies which have reported that most patients with EP tend to be of low parity. Miyoro et al. reported that 77.2% of the cases were para  $\leq 2$  (4). Parazzini reported similar association in Italy (10).

Majority (42.4%) of the LNG-EC users were aged 20-24 years, were nulliparous (51.5%) and had college level education (45.5%). This is in keeping with the ACOG practice bulletin report of May 2010 (16), which described EC users as being below 25 years and had never been pregnant. A study done in Hong Kong between 2006-2008 to describe characteristics of EC users (49) however reported a mean age of 30years, with 65.5% being nulliparous.

Only 18.2% of the cases who took the pill knew their fertile days. Seventy two percent (72.2%) of the cases took the pill within 24 hrs of unprotected coitus and all the 3 controls took the pill within 24-48 hrs. Majority of the cases (78.8%) and all the controls swallowed both pills at once and most women (n=24 cases and n=3 controls) swallowed the pill in the secretory phase.

From this study therefore, majority of the women knew the correct timing and dosing of use of LNG-EC and used it correctly compared to a study done among Kenyatta University students by Nyawande et.al. in 2005 where despite significant knowledge of the fertile days (81%), only 52% knew how the correct timing (30). This increase in knowledge of the timing could be attributed to a robust media campaign carried out by PSI to educate women of reproductive age on the correct use of the emergency pill over the last few years.

The most effective period of action of POEC has been described as the pre-ovulatory follicular phase with reports of delay of ovulation by upto 5 days by 100% (31, 32, 33), majority of the cases who took the pill (n=24) in this study and all the controls (n=3) took the pill in the secretory phase. Pulkinen and Talo (35,36) described the myoelectrical activity of the fallopian tube, and reported that progesterones inhibit tubal motility post fertilization and could cause a delay in ovum transport resulting in EP.

Other risk factors for EP were also assessed. From this study, early age at sexual debut increased the risk of EP. The risk increased seven fold in women report their first sexual contact before their 15<sup>th</sup> birthday compared to those who had their first contact at 25 years and above. Sixty two percent (62.5%) of the cases had their sexual debut before their 20<sup>th</sup> birthday compared to 51.2% of the controls. A recent study in China showed a fourteen –fold increase in the risk of EP in patients who had their sexual debut before 18 years (51). This is explained by the immaturity of the vaginal epithelium in younger people making them more susceptible to ascending infections with long term sequelae.

Patients who conceived after a period of infertility/ subfertility were five times more likely to have an EP from this study. Twenty one percent (21%) of the cases reported a period of inability to conceive for at least 6 months after stopping use of contraceptive method versus 5% of the controls. Parazzini in an Italian case control study reported a three times higher risk of EP among the cases (10). The cause of the infertility would most likely be implicated in the etiology of the EP.

There was no association between the previous use of IUCD or other long term methods of family planning. This is in keeping with findings of Miyoro et al. in 2002 in the same facility where he reported no association between IUCD and ectopic pregnancy (4). Only one (0.8%) patient recruited during the study period conceived with an IUCD in situ and the pregnancy was an EP. The study done in China reported that previous use of IUCD was not significantly associated with EP. However in case of contraceptive failure with an IUCD in situ, the risk of EP was 21.08 higher than with no contraceptive method at the time of conception (51). One patient (0.8%) conceived while on the minipill during the entire study period. The resulting pregnancy was an EP. Progesterone only pills have been reported to slightly increase the risk of EP upto 4-6% (1, 11). However from this study there was no significant association.

Sexually transmitted infections have a well documented role in causation of EP. The risk in this study increased three-fold with 25% of cases reporting history of treatment for an STI compared to 10.1% of the control group. Miyoro et al. in their study reported that 56.6% of the cases had features suggestive of PID (4). Parazzini in an Italian study reported a six-fold increase in the risk of EP in patients who had been treated for an STI/PID (10), double what was reported in our study. Nathalie et al. in a review of several African studies concluded that PID resulting from STI's was the single most important risk factor for the development of EP in African developing countries (7). The widespread use of antibiotics in treatment for STI's allows some degree of patency to be maintained in the fallopian tubes resulting in EP.

This study did not show any association between EP and history of previous abdominal pelvic surgery as reported in other studies. Twenty percent (20%) of the cases and 27 % of the controls had a previous abdominopelvic surgery with majority having undergone a caesarean section.

The Italian study reported an 8-fold increase in ectopic pregnancy among patients with an EP compared to the controls (10). Our study however had a highly selected group in terms of previous caesarean section among the control. KNH being a national referral hospital does not attend to low risk antenatal mothers, who tend to receive antenatal care in smaller facilities within the county. Women with previous caesarean sections are usually referred for antenatal care and delivery to KNH which could explain the higher number of women with previous surgery in the control group compared to those in the cases.

There was no association between previous history of tuboplasty and risk of EP. However only 3.3% of the cases and 1.7% of the controls had undergone tuboplasty making it difficult to draw any statistical association. This could possibly due to the low success rates of tuboplasty. Other studies have shown significant association in patients who had previous tuboplasty or reversal of tubal ligation who eventually conceived (10).

## **CONCLUSION:**

1. Failed POEC increases the risk of ectopic pregnancy
2. Early sexual debut, infertility/subfertility and previous STI rx are significant risk factors for ectopic pregnancy.

**RECOMMENDATION:**

1. POEC should be recognized as a risk factor for EP and included in the client information leaflet in the drug packaging.
2. Client education at the point of sale using IEC materials and advise on when to seek medical attention



## **STUDY TIMELINES**

Ethical approval	September 2014
Data collection	October 2014 to January 2015
Data analysis	February to March 2015
Result presentation to faculty	March 2015

## **BUDGET**

<b>ITEM</b>	<b>UNIT COST (KSHS)</b>	<b>TOTAL (KSHS)</b>
Printing & binding	10,000	10,000
2 research assistants	10,000	20,000
Airtime/ communication	5,000	5,000
Statistician	20,000	20,000
Stationery	5,000	5,000
Final dissertation booklet	6,000	6,000
Ethics and research committee fee	2,000	2,000
Miscellaneous	20,000	20,000
<b>TOTAL</b>		<b>88,000</b>

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## **APPENDICES**

### **APPENDIX 1:**

#### **INFORMED CONSENT FORM**

#### **ASSOCIATION BETWEEN HORMONAL EMERGENCY CONTRACEPTIVE PILL AND THE RISK OF ECTOPIC PREGNANCY**

##### **Investigator:**

Dr Mary Wanjiku Maina  
Resident, Department Of Obstetrics and Gynaecology  
University of Nairobi  
P.O Box 342,00200 Nairobi  
Mobile No: 0722 327 304

##### **Supervisor:**

Professor Joseph Karanja  
Associate professor,  
Department of Obstetrics and gynaecology  
University of Nairobi  
Mobile No : 0722 513 881

##### **Investigators statement**

I am asking you to be in a research study. The purpose of this consent form is to give you the information you will need to decide whether to be in the study or not. Please read this form carefully. You may ask questions about what you will be asked to do, the risks, the benefits and your rights as a volunteer, or anything about the research that is not clear in this form. When all your questions have been answered, you can decide if you want to be in this study or not. This process is called “informed consent”.



### **Purpose and Benefits**

This study seeks to establish whether there is a relationship between the use of an emergency contraceptive pill that contains a hormone known as progesterone and the occurrence of a pregnancy that is outside the womb, also known as an ectopic pregnancy, and to also evaluate other risk factors associated with such a pregnancy.

Participants will receive free health education on risks factors for ectopic pregnancy and on the correct use of emergency contraceptive pills.

### **Risks, Stresses and Discomfort**

There are no risks involved from participating in the study. Some of the questions asked will be of personal nature, you are however encouraged to answer all of them. You will receive the care that is expected. Completing the questionnaire will take you 10-20 minutes.

### **Expectations**

By agreeing to participate you are expected to answer questions regarding your biodata, medical and obstetric history. You are also agreeing to let the study team obtain information from your medical records about any further information that may be required

### **Cost**

Cost of standard care will be incurred by the patient herself

### **Confidentiality**

Your confidentiality will be maintained at all times. The questionnaires will not have any names but will be assigned identifiers. Only the investigator, the university of Nairobi Ethics and Research committee will have access to information about you.

There shall be no mention of names or identifiers in the report or publications which may arise from the study. The information obtained will be used only for the purpose of the study.

You may withdraw from the study or refuse to answer any of the questions asked at any time without the loss of benefit or any penalty.

Your participation to the study is voluntary and will be highly appreciated

**DECLARATION**

I have explained to the respondent the nature and purpose of the study as described above. The respondent has been informed of their right to ask questions and I have clarified any issues to the best of my ability.

Investigator's Signature : -----Date:-----

**CONSENT TO PARTICIPATE IN THE STUDY**

**Participant's statement:**

This study has been explained to me. I volunteer to take part in this research. If i have questions later on about the research i can ask the investigator above.

If i have questions about my rights as a research subject i can call the university of Nairobi ethics and research committee on 2726300. I will receive a copy of this consent form.

Signature of participant : ----- Date.....

Name of participant : -----

Incase of any Ethical concerns please contact:

The Chairperson- **Professor A.N. Guantai**

Kenyatta National Hospital/University of Nairobi Ethics and Research Committee

Hospital Road along Ngong Road

P.O. Box 20723, Nairobi

Telephone 2726300 Ext: 44102

Copies to :1. participant    2. Investigators file

**APPENDIX II: QUESTIONNAIRE**

Patient's study number.....

**Biodata**

1. Age :

- ≤19 years
- 20- 24 years
- 25-29 years
- 30-34 years
- ≥35 years

2 .Marital status:

- single
- married
- separated
- divorced
- widowed

3.Level of education:

- Primary
- secondary
- college
- university

**OBS/GYN HISTORY:**

4.parity:

- 0
- ≥5
- 1-2
- 3-4

5.History of use of emergency contraceptive pill during the menstrual cycle leading to this pregnancy

- Yes
- no

6.If yes to no 5, where did you obtain the pills from:

Pharmacy/chemist                       hospital                       friend                       others  
(specify).....

7. What did you ask for from the provider of the drugs ( e-pill, p2 etc)..... (write down what patient says)

8. Were you given instructions on how to take the drug?

yes     no

if yes, specify the instructions given .....

9. If yes to no 5;

How long after coitus did you take the drug

<24 hours                                       24-48 hrs  
 48-72 hrs                                       >72 hrs

10. What is your menstrual cycle length?

Specify no. of days .....                       Irregular                       I don't know

(if patient knows dates, calculate her cycle length)

11. if yes to no 5 above;

On which day of your menstrual cycle did you take the drug ( based on the day, investigator/assistant to determine the phase of the cycle)?

Follicular                                       ovulatory                                       secretory

12. if yes to no 5 above;

How did you take the drug?

Both at once                                       swallowed at interval (specify interval in hours).....

14. How many times had you used the emergency pill in the one month preceding this pregnancy?

Specify no of times.....

15. At what age was your first sexual encounter?

Specify.....

16. How many sexual partners have you had so far ?

Specify.....

17. Was this pregnancy planned?

Yes  no

18. If yes to no 13, was it timely?

Yes  no

19. Long term method of contraceptive 1 year prior to conception :

None  pills  IUCD  implant  
injectable

20. Have you ever been treated for an STI/abnormal vaginal discharge (exclude candidiasis)

Yes  no

If yes, how many times

Once  more than once (specify).....

21. Do you have a history of inability to conceive for > 6 months since you stopped your regular contraceptive method?

Yes (specify no. of months/years)..... No

22. Do you have a history of tuboplasty ?

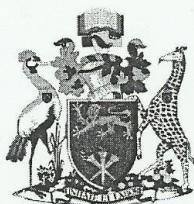
Yes

no

23. Do you have previous history of abdominal/pelvic surgery ?

Yes (specify type of surgery).....

No



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Link: [www.uonbi.ac.ke/activities/KNHUoN](http://www.uonbi.ac.ke/activities/KNHUoN)

6<sup>th</sup> October 2014

Dr. Mary Wanjiku Maina  
Dept. of Obs/Gynae  
School of Medicine  
University of Nairobi

Dear Dr. Maina

**RESEARCH PROPOSAL: ASSOCIATION BETWEEN PROGESTERONE ONLY EMERGENCY CONTRACEPTIVE PILL AND THE RISK OF ECTOPIC PREGNANCY (P437/07/2014)**

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This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and approved your above proposal. The approval periods are 6<sup>th</sup> October 2014 to 5<sup>th</sup> October 2015.

This approval is subject to compliance with the following requirements:

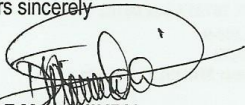
- a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
- b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
- c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
- d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
- e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal.*)
- f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
- g) Submission of an *executive summary* report within 90 days upon completion of the study  
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website [www.uonbi.ac.ke/activities/KNHUoN](http://www.uonbi.ac.ke/activities/KNHUoN).

Protect to discover



Yours sincerely



**PROF. M.L. CHINDIA**  
**SECRETARY, KNH/UON-ERC**

- c.c. The Principal, College of Health Sciences, UoN
- The Deputy Director CS, KNH
- The Chair, KNH/UoN-ERC
- The Assistant Director, Health Information, KNH
- The Dean, School of Medicine, UoN
- The Chairman, Dept. of Obs/Gynae, UoN
- Supervisors: Prof. Joseph Karanja, Dr. Peter Michoma

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