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DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
DÉPARTEMENT DE GYNÉCOLOGIE OBSTÉTRIQUE

INTRAUTERINE ECTOPIC PREGNANCY: ASSOCIATED FACTORS AND OUTCOME OF SUBSEQUENT PREGNANCIES, A FIVE YEARS RETROSPECTIVE STUDY IN TWO HOSPITALS IN YAOUNDE.

Dissertation submitted in partial fulfilment of requirements for the award of a Specialist Diploma (DES) in Obstetrics and Gynaecology

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DEDICATION

This dissertation is dedicated to

GOD almighty

For his continuous guidance and protection.

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ABSTRACT

Background: Ectopic pregnancy [EP] is the implantation of a developing blastocyst out of the normal site in the endometrial cavity. The most common site of EP is the fallopian tube, but other sites could be involved. Intrauterine ectopic pregnancies (IUEP) are rare but its mortality is about 6-7 times higher than in tubal EP. Invasive management technics are usually done and this could compromise the fertility, obstetric or vital prognosis of these patients in subsequent pregnancies.

Objective: to study the factors associated with occurrence of IUEP and the outcome of pregnancies following these IUEP in 2 hospitals in Yaounde.

Methods: this was a case-control study carried out on a 5 years period. An exhaustive consecutive sampling method was used, with a case vs control matching ratio of 1 IUEP:3 tubal EP. P-values obtained from Chi-square test for proportions and Student's t-test for means. Univariate and Multivariate analysis by logistic regression done to assess associated factors and control the effect of confounders and Odd's ratios obtained. Statistical significance was set at 5%.

Results: we found a total of 1014 EP amongst which 78 were intrauterine (cornual or interstitial), excluded 37 cases and 41 cases matched against 123 controls. The proportion of IUEP amongst all EP was 7.7%, only 10.5% had an exact ultrasound diagnosis and 85.4% of them presenting in a haemodynamic unstable state. There was a significant association between IUEP and 4 factors, out of which 3 were independently associated, 2 with increased odds of IUEP; history of ipsilateral salpingectomy ap= 0.042, [aOR: 6.41; 95%CI: 1.07-60.51] and age ≥31 years ap=0.010, [aOR: 2.42; 95%CI: 1.23-4.74] and 1 with decreased odds of IUEP, history of PID ap=0.014, [aOR: 2.66; 95%CI: 1.22-5.81]. Passed history of EP was associated with increased odds of IUEP but not independently p=0.024, [OR: 3.41; 95%CI: 1.12-10.42]. Out of the 17 patients that conceived, 10 had reached at least 30 weeks of gestation with 3 still pregnant and 7 had a term delivery; of which 3 were vaginal and 4 by caesarean section. We recorded no uterine rupture.

Conclusion: IUEP is fairly common, its exact diagnosis is difficult and management late. The presence of the following associated factors; age ≥31 years, previous ectopic pregnancy and history of ipsilateral salpingectomy should raise a high index of suspicion of an IUEP by clinicians. The outcome of subsequent pregnancies is favourable with caesarean section being the most frequent delivery route.

Key words: intrauterine, ectopic, pregnancy, factors, outcome, Yaounde.

RÉSUMÉ

Contexte : La grossesse extra-utérine (GEU) est l'implantation d'un blastocyste en développement hors de son site normal dans la cavité endométriale. La trompe de Fallope est le site où la GEU est le plus souvent localisée, mais celle-ci peut également s'implanter à d'autres endroits. Les grossesses ectopiques intra-utérines (GEIU) sont rares, mais leur taux de mortalité est environ 6 à 7 fois plus élevé que celui des GEU tubaires. Des techniques de prise en charge invasives sont généralement utilisées, ce qui peut compromettre la fertilité, le pronostic obstétrique ou vital des patientes lors de grossesses ultérieures.

Objectif : étudier les facteurs associés à la survenue d'une GEIU et l'issue des grossesses consécutives à ces GEIU dans deux (2) hôpitaux de Yaoundé.

Méthodes : il s'agit d'une étude cas-témoins réalisée une période de 5 ans. Une méthode d'échantillonnage exhaustive et consécutive a été utilisée avec un appariement cas-témoin au ratio 1GEIU:3G-tubaire. Les valeurs p obtenues à partir des tests chi carré pour les proportions et du test t de Student pour les moyens. Des analyses univariée et multivariée par régression logistique ont été effectuée pour évaluer les facteurs associés et contrôler l'effet des facteurs de confusion et les rapports de côtes obtenu. La signification statistique a été fixée à 5 %.

Résultats : des 1014 GEU recensé, 78 étaient intra-utérines (cornuales ou interstitielles), 37 cas exclu et 41 cas appariés à 123 témoins. Les GEIU représentent 7,7 % de l'ensemble des GEU, seul 10.5% avait un diagnostic échographique exact et 85,4 % des patientes étaient en état d'instabilité hémodynamique. Une association significative a été observée entre les GEIU et 4 facteurs, dont 3 étaient associés de manière indépendante, 2 avec un risque accru de GEIU ; antécédent de salpingectomie ipsilatérale ap= 0,042 [aOR : 6,41 ; 95%CI : 1,07-60,51] et l'âge ≥31 ans ap=0, 010 [aOR 2,42 ; 95%CI : 1,23-4,74] et 1 avec une diminution du risque de GEIU, antécédent de PID ap=0, 014, [aOR : 2,66 ; 95%CI : 1,22-5,81]. Les antécédents de GEU étaient associés avec un risque accru de GEIU, mais pas de manière indépendante p=0,024 [OR : 3,41 ; 95%CI : 1,12-10,42]. Sur les 17 patientes ayant conçu, 10 avaient atteint au moins 30 semaines de gestation, 3 étaient encore enceintes et 7 ont accouché à terme, dont 3 par voie basse et 4 par césarienne. Aucune rupture utérine n'a été constatée.

Conclusion : Les GEIU sont assez fréquentes, leur diagnostic exact est difficile et leur prise en charge tardive. La présence de facteurs associés (âge ≥31 ans, grossesse extra-utérine antérieure et antécédents de salpingectomie ipsilatérale) doit éveiller les soupçons du clinicien quant à l'existence d'une GEIU. L'issue des grossesses ultérieures est favorable, la césarienne étant la voie d'accouchement la plus fréquente.

Mots clés : Intra-utérine ; Ectopique ; Grossesse ; Facteurs ; Issue, Yaoundé.

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LIST OF ABBREVIATIONS

AOR	Adjusted Odd Ratio
ART	Artificial Reproductive Technic
B-HCG	B-Human Chorionic Gonadotropin
CEP	Cervical Ectopic Pregnancy
CI	Confidence Interval
CP	Cornual Pregnancy
CSP	Cervical Scar Pregnancy
CSPro	Census and Survey Processing System
D&C	Dilatation and Curettage
DMPA	Depot Medroxyprogesterone Acetate
EP	Ectopic Pregnancy
EUEP	Extrauterine Ectopic Pregnancy
ICSI	Intra-Cytoplasmic Sperm Injection
IP	Interstitial Pregnancy
IRB	Institutional Review Board
IUD	Intra Uterine Device
IUEP	Intra Uterine Ectopic Pregnancy
IVF	In Vitro Fertilization
IVF-ET	In Vitro Fertilization Embryo Transfer
LNG-EC	Levonorgestrel Only Pill Emergency Contraception
MTX	Methotrexate
NTEP	Non-Tubal Ectopic Pregnancy
OR	Odd Ratio
PID	Pelvic Inflammatory Disease
SPSS	Statistical Package for The Social Sciences
STI	Sexually Transmissible Infection
TVUS	Transvaginal Ultrasound
UAE	Uterine Artery Embolization
YCH	Yaounde Central Hospital
YGOPH	Yaounde Gynaeco-Obstetric and Paediatric Hospital

CHAPTER I : INTRODUCTION

I.1. BACKGROUND

Ectopic pregnancy (EP) is the implantation of a developing blastocyst out of the normal site in the endometrial cavity[1]. Although the most common site of EP is the fallopian tube, other sites could be involved. Non-tubal ectopic pregnancies (NTEP), can be in the corneum or interstitium, serosal lining of the uterus, endocervical canal, myometrium (inside an area of adenomyosis), ovary or abdominal cavity[2].

EP accounts for about 2% of all pregnancies [2]. Over the last few decades, the incidence of EP has steadily increased around the world. In the Western countries, it varies between 1–2% but even higher in developing countries, especially in Cameroon where it reaches 4.23%[3]. About 5% of all ectopic pregnancies have a non-tubal localization[4]. Intrauterine ectopic pregnancies are rare; with interstitial or cornual ectopic pregnancies accounting for 2 to 5% of all ectopic pregnancies[1] and cervical ectopic pregnancies (CEP) accounting for less than 1% of all ectopic pregnancies[4].

Although intrauterine ectopic pregnancy (IUEP) is rare, its morbi-mortality is high; uterine rupture may occur in up to 20% of the cases of cornual pregnancies that progress beyond 12 weeks of amenorrhea, resulting in massive haemorrhage due to high vascularity in this region from the branches of the uterine and ovarian arteries. Consequently, cornual resection is usually required[5]. In a similar manner CEP may present with life-threatening unexpected bleeding due to erosion of the cervical blood vessels and may require a hysterectomy[6]. Ectopic pregnancy is the main cause of maternal death during the first trimester of pregnancy, accounting for approximately 10% of all pregnancy-related deaths[3]. In African developing countries, most women tend to present at the rupture stage (with hemodynamic instability). Recently in Cameroon, it was reported to be responsible for 12.5% of maternal deaths[7]. The case fatality rates are around 1–3% in African countries, about 10 times higher than reported in industrialized countries[3,8]. Cornual pregnancy is reported to have a mortality rate of 2 to 3% [1], about 6-7 times higher than in tubal EP[9].

We found few publications on factors associated with these rare forms of ectopic pregnancy. Risk factors for CEP are reported being previous uterine operations, ART (artificial reproductive techniques) and Asherman's syndrome[4]. Risk factors for interstitial or cornual ectopic pregnancy are generally similar to those of all ectopic pregnancies amongst which we have; pelvic inflammatory disease, previous pelvic or abdominal cavity surgery, uterine anomalies or malformations, uterine tumours, and assisted reproductive technologies[9]. However in another review ipsilateral salpingectomy is thought to be the only known etiological factor specific to interstitial ectopic pregnancy[1].

Literature is unclear on fertility and obstetrical outcomes following cornual pregnancy. In some they are not affected whatever the initial treatment[10]. In others after medical treatment for an interstitial pregnancy, the risk of uterine rupture remains unknown for a future pregnancy, even though this concern exists for interstitial pregnancies that are treated surgically, warranting close monitoring of these women during pregnancy and elective caesarean section for delivery [11,12].

There is high morbidity and mortality associated with IUEP due to its implantation zone and proximity to the major uterine blood vessels and its susceptibility to rupture at a later gestational age which may cause severe haemorrhage[9]. Therefore, increased awareness and knowledge on its associated factors could help by providing better prediction and prevention in women at risk. This could also enable an early and accurate diagnosis prior to the rupture, and results in a reduction in the need for surgery and other complications. Knowledge of outcome needed for counselling of patients on preventive measures to be taken in subsequent pregnancies.

I.2. JUSTIFICATION

We found a scanty literature in our environment on factors associated with Intrauterine ectopic pregnancy and on the outcome of pregnancies occurring after these ectopic pregnancies. These very rare forms of ectopic pregnancies have a severe impact on the vital, fertility and obstetric prognosis of affected women. Hence, the need to investigate on factors associated to these pregnancies and outcome of subsequent pregnancies which could help promote early diagnosis and prompt management.

I.3. RESEARCH QUESTION

Main; what are the factors associated with intrauterine ectopic pregnancy and what is the outcome of subsequent pregnancies within the past 5 years.

I.4. RESEARCH HYPOTHESIS

Ha; there are socio-demographic and clinical factors associated with intrauterine ectopic pregnancies and the outcome of pregnancies following IUEP can be unfavourable.

I.5. RESEARCH OBJECTIVES

GENERAL; Study the factors associated with occurrence of IUEP and the outcome of pregnancies following these IUEP.

SPECIFIC OBJECTIVES;

1) Describe the distribution of ectopic pregnancies by sites
2) Determine the socio-demographic factors associated with intrauterine ectopic pregnancy
3) Identify the clinical factors associated with intrauterine ectopic pregnancy
4) Evaluate the outcome of subsequent pregnancies

I.6. RESEARCH GOAL

Identification of factors associated with Intrauterine ectopic pregnancy will help reduce further the prevalence of intrauterine ectopic pregnancies, favour early diagnosis and management hence ameliorating the fertility, obstetric and vital prognosis of patients.

I.7. SCOPE OF STUDY

This study will focus on files of patients with ectopic pregnancy managed surgically in these 2 hospitals.

I.8. DEFINITION OF OPERATIONAL TERMS

1. **IUEP:** Intrauterine ectopic pregnancy confirmed by postoperative note (cornual/interstitial, cervical).
2. **Cohabiting**: Couple living together for at least 1 month.
3. **Rural area**: Zone out of the 7 subdivisions of Yaounde.
4. **Urban**: Zone within the 7 subdivisions of Yaounde.
5. **Ovulation induction**: Any drug used to stimulate ovulation
6. **Incomplete files**: Those without information on passed medical history.
7. **Late diagnosis**: Diagnosis of ectopic pregnancy when rupture has occurred.
8. **Fertility desire**: Women of child bearing age who want to have more children.
9. **Unfavourable outcome**: Occurrence of uterine rupture

CHAPTER II : LITERATURE REVIEW

II.1. OVERVIEW

II.1.1. Background

Ectopic pregnancy [EP] is the implantation of a developing blastocyst out of the normal site in the endometrial cavity[1]. It could be located in the fallopian tube or outside the fallopian tube. Non-tubal ectopic pregnancies [NTEP], which can be in sites such as intramural (within the serosal lining of the uterus), cornual (also called interstitial by some authors), in the endocervical canal, intramyometrial (inside an area of adenomyosis), extramural (outside the serosal lining of the uterus), ovarian or abdominal pregnancies[2]. Compared with tubal ones, extratubal EP are atypical in history or symptoms, appear belatedly rendering early diagnosis extremely difficult and could be more dangerous[13].

II.1.2. Epidemiology

❖ Incidence

EP accounts for about 2% all pregnancies [2]. Over the last few decades, the incidence of EP has steadily increased around the world. In the Western countries, it varies between 1–2% yet higher in developing countries, especially in Cameroon where it reaches 4.23%[3]. About 5% of all ectopic pregnancies have a non-tubal localization[4]. Intrauterine ectopic pregnancies are rare; interstitial or cornual ectopic pregnancies accounting for 2 to 5% of all ectopic pregnancies[1] and cervical ectopic pregnancy (CEP) accounting for less than 1% of all ectopic pregnancies[4].

❖ Morbi-mortality

Though Intrauterine ectopic pregnancy (IUEP) is rare, its morbi-mortality is high; uterine rupture may occur in up to 20% of the cases of cornual pregnancies that progress beyond 12 weeks of amenorrhea, resulting in massive haemorrhage due to high vascularity in this region through the branches of the uterine and ovarian arteries and consequently cornual resection[5]. In a similar manner CEP may present with life-threatening unexpected bleeding due to erosion of the cervical blood vessels and may require a hysterectomy[6]. Ectopic pregnancy is the main cause of maternal death during the first trimester of pregnancy, accounting for approximately 10% of all pregnancy-related deaths[3], in African developing countries, where most women tend to present at the rupture stage (with hemodynamic instability), recently in Cameroon, it was reported to be responsible for 12.5% of maternal deaths[7]. The case fatality rates around 1–3% in African countries about 10 times higher than reported in industrialized countries[3,8]. Non-tubal ectopic pregnancies have a high mortality rate notably cornual pregnancy reported having a mortality rate of 2 to 3% [1,6] about 6-7 times higher than in tubal pregnancies[9].

❖ **Risk Factors**

We found few publications on factors associated with these rare forms of ectopic pregnancy. Risk factors for non-tubal ectopic pregnancy are generally similar to those of all ectopic pregnancies amongst which we have; pelvic inflammatory disease, previous pelvic or abdominal cavity surgery, uterine anomalies or malformations, uterine tumours, and assisted reproductive technologies[2,9,13]. However in another review Ipsilateral salpingectomy is thought to be the only known etiological factor specific to interstitial ectopic pregnancy[1,14]. Other reviews report CEP risk factors to be; previous uterine operations, ART (artificial reproductive techniques) and Asherman's syndrome[4].

Previous ectopic pregnancy: The risk of repeat ectopic pregnancy in patients with a prior ectopic gestation is approximately 3-8-fold higher compared with other pregnant patients. This risk is related to both the underlying tubal disorder that led to the initial ectopic pregnancy and to the choice of treatment procedure. History of salpingostomy for ectopic pregnancy is a risk factor for recurrent ectopic pregnancy. In a series of 32 interstitial pregnancies, the most common risk factors (40.6%) were tubal damage from previous ectopic pregnancy[15].

Previous salpingectomy: tubectomy in some studies was identified as risk factor for ectopic pregnancy[16] and also a risk factor for recurrent EP[17]. The incidence of IP dramatically increased after salpingectomy when performed in subjects with hydrosalpinx or tubal pregnancy before IVF embryo transfer. The incidence of EP can reach up to 11% in female patients with a history of tubal factor infertility[14].

Pelvic inflammatory diseases (PID): Pelvic infection (e.g., nonspecific salpingitis, chlamydia, gonorrhoea or specific as tuberculosis), especially recurrent infection is responsible for causing peritubal adhesions, partial closure of lumen, intra-tubal adhesions, diverticuli and cysts. In the diverticuli the myoelectrical activity is diminished and limited to that segment of the tube only and therefore the fertilized ovum gets trapped in it[18]. gonococcal, chlamydial and other bacterial infection causes a 3.3- 6fold increased risk of ectopic pregnancy[16]

History of D and C: Improper hygiene and sepsis while performing D and C can lead to PID. Also, overzealous curettage can lead to endometrial lesions and adhesions increasing the risk of ectopic pregnancy[18]. In a study conducted in Nigeria induced abortion was found to be the most common risk factor for ectopic pregnancy[19] and also a factor for recurrence[17].

History of previous abdominal surgery: The cause of ectopic pregnancy following abdominal surgery was observed by some authors to be peritubal adhesions and scarring[18].

Infertility: The incidence of ectopic pregnancy is approximately 2-3 fold higher in patients with infertility, although this could reflect the increased incidence of tubal abnormality in this group of patients, which may also be an aetiology of infertility[20].

ART: has been associated with an increased risk of both ectopic and heterotopic pregnancy[21]. Blastocyst single embryo transfer significantly reduced the risk of EP. Transfer of embryo on day 5 can reduce the migration time of the embryo and ensure rapid implantation in the endometrium, reducing the rate of EP. ICSI is thought to be associated with a reduced incidence of EP when compared with IVF. The technique of embryo transfer is also a potential cause of IP, but there is little evidence to support this possibility, such as uterine contractions caused by the transfer procedure. Deep insertion of the transfer tube, having the catheter tip comes into contact with the uterine fundus may cause uterine contraction. And high oestrogen and progesterone levels, which affect endometrial receptivity. Authors from a recent study proposed an "embryo factor"; IVF embryos might be exposed to a different growth factor and cytokine milieu during in-vitro culture compared with naturally conceived embryos. Therefore, such embryos might be unable to implant within the uterus during its receptive period and instead migrate into the fallopian tube and attach to the tubal epithelium. Several reports have also suggested an association between fertility drugs and ectopic pregnancy, which may be related to altered tubal function secondary to hormonal fluctuation. In a randomized study, incidence of ectopic pregnancy was comparable in comparing gonadotropin, clomiphene, or letrozole and the rates are higher than that in the general population[14,20,22].

Tubal reconstructive surgery: Patients with tubal damage or sterilization may undergo tubal reconstructive surgery to attempt to restore tubal fertility, although this has largely been replaced by IVF. The risk of ectopic pregnancy is high after tubal reconstructive surgery, and the outcome depends upon the function and condition of the tube, type of surgery, and surgeon's expertise. Rates of ectopic pregnancy after tubal reconstructive surgery range widely, from 3 to 30%[23].

Contraceptive methods: Patients using contraception are at very low risk of conceiving any pregnancy, either intrauterine or ectopic. However, if they conceive, the probability of an ectopic pregnancy is generally higher than in patients not using contraception.

a. **Sterilization**: The risk of ectopic pregnancy in patients who undergo sterilization and then experience sterilization failure is 5- to 19-fold higher than the risk in other pregnant patients.

b. **Intrauterine devices**: Patients using an IUD have a lower incidence of ectopic pregnancy than non-contracepting patients because the IUD is a highly effective method of contraception. The estimated absolute risk of ectopic pregnancy in copper IUD users is approximately one-half the risk in patients who are not using any type of contraceptive. Among IUD users with contraceptive failure, the risk of ectopic pregnancy is high (1 in 2 pregnancies for the levonorgestrel IUD and 1 in 16 pregnancies for the copper IUD versus 1 in 50 pregnancies among non-contraceptors).

c. **Progestin-only contraceptives**: Progestin-only injection and levonorgestrel emergency pills appear to be associated with an increased risk of ectopic pregnancy[3].

Smoking: Cigarette smoking in the periconceptional period is associated with a dose dependent increase in the risk of ectopic pregnancy. A history of smoking is associated with a two- to threefold increase in ectopic pregnancy risk and current use is associate with a two- to fourfold risk. A possible explanation for this finding may be impaired in tubal motility in smokers or impaired immunity, thus predisposing them to pelvic inflammatory disease[3].

Increasing age: There is an increasing proportion of ectopic pregnancies among patients in the older age groups. This high incidence in older patients may be a reflection of cumulative risk factors over time and chromosomal abnormalities[20].

II.2. ANATOMY OF THE FEMALE REPRODUCTIVE SYSTEM

The female reproductive system is made up of; external female Genitalia (Vulva, Clitoris) and internal genitalia (Vagina, Cervix, Uterus, Fallopian tubes, Ovaries) and an accessory organ (Breasts).

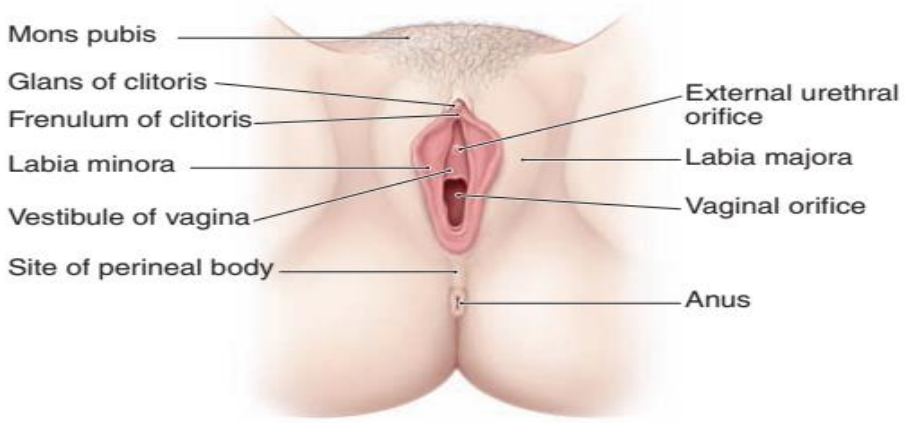

Figure 1 : External female genitalia

(Source: *Obstetrics and Gynecology;* 6th edition Charles R.B. Beckmann page 36)

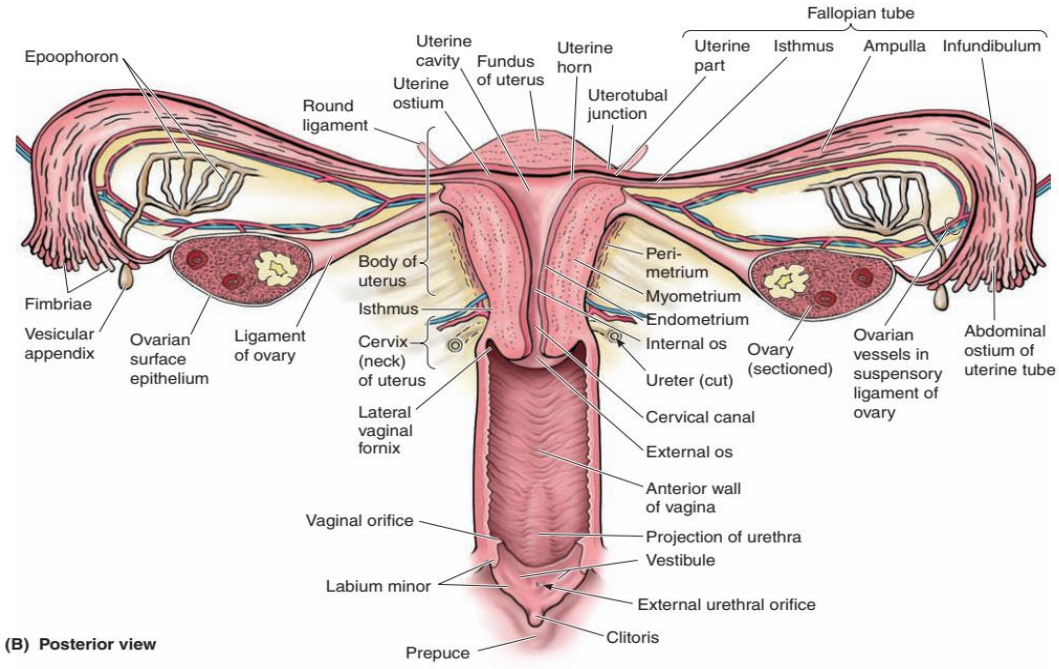

Figure 2 : Internal female reproductive organs

(Source: *Obstetrics and Gynecology;* 6th edition Charles R. B. Beckmann page 38)

❖ **Vulva**

It contains the labia majora, labia minora, mons pubis, clitoris, vestibule, and ducts of glands that open into the vestibule.

Mons Pubis: A prominence caused by a pad of fatty tissue over the symphysis pubis. It is covered by hairs at puberty (pubic hair).

labia majora are folds of skin with underlying adipose tissue, fused anteriorly with the mons pubis and posteriorly at the perineum. The skin of the labia majora contains hair follicles as well as sebaceous and sweat glands.

Labia minora are narrow skin folds lying inside the labia majora. The labia minora merge anteriorly with the prepuce and frenulum of the clitoris, and posteriorly with the labia majora and the perineum. The labia minora contain sebaceous and sweat glands, but no hair follicles, and there is no underlying adipose tissue.

Clitoris is located anterior to the labia minora, is the embryologic homolog of the penis. It consists of two crura (corresponding to the corpora cavernosa in the male) and the glans, which is found superior to the point of fusion of the crura.

Frenulum is on the ventral surface of the glans**,** the fused junction of the labia minora.

Vestibule lies between the labia minora and is bounded anteriorly by the clitoris and posteriorly by the perineum. The urethra and the vagina open into the vestibule in the midline. The ducts of Skene (paraurethral) glands and Bartholin glands also empty into the vestibule.

Introitus (vaginal orifice): It is an orifice in the vestibule that opens into the vagina. It is partially covered by the hymen, a thin membranous fold highly variable in appearance. Its rupture may occur for a variety of reasons. It is sometimes absent (even in some virgins).

Bartholin's Glands (vestibular glands): 2 glands at the 4 and 8 o'clock positions of the introitus (equivalent of Bulbourethral gland in male). Produce secretions that lubricate the vagina during sexual intercourse and birth. Can be blocked resulting in a cyst or an abscess (if infected).

Urethral opening: It is the opening into the urethra and located between the clitoris and introitus.

Skene glands (female urethral glands): Numerous mucous glands in wall of female urethra.

❖ **The Vagina**

The vagina is a 6-10cm long muscular hollow organ that extends from the vestibule to cervix of the uterus, located between the bladder and urethra anteriorly and the rectum posteriorly. It serves to receive erect penis during sexual intercourse and to convey uterine secretions to the exterior. The vagina serves as passage for the offspring during birth. Its posterior wall (7-10cm) is longer than the anterior wall (6-8cm). The cervix enters the vagina at the superior 1/3rd dividing it into 4 compartments called fornices (2 lateral, 1 anterior and 1 posterior). The posterior fornix is the largest and can be used to access the abdominal cavity**.** The vagina has 3 layers;

1. The inner mucosa layer which is highly folded and can loosen up during sexual intercourse to accommodate the penis (about 15 cm). At puberty, oestrogen causes accumulation of glycogen which is metabolized to lactic acid giving the vagina an acid pH of 3.5-4.0 that promotes growth of harmless bacteria known as Doderlein's bacteria (Gram positive bacilli)

2. The middle muscular layer made up of 3 layers of muscles.

3. The outer serous layer of connective tissue.

❖ **The Uterus**

The uterus is pear-shaped organ and consists of two major but unequal parts: an upper triangular portion-the body or corpus, and a lower, cylindrical portion-the cervix, which projects into the vagina. The isthmus is the union site of these two. It is of special obstetric significance

because it forms the lower uterine segment during pregnancy. The uterus, along with the proximal portion of the vagina and fallopian tubes, is embryologically derived from the paramesonephric ducts. The nonpregnant uterus is situated in the pelvic cavity between the bladder and the rectum.

Uterine cornu located at each superolateral margin of the body, from which a fallopian tube emerges. Also in this area are the origins of the round and utero-ovarian ligaments. The fundus describes the convex upper uterine segment that lies cephalad to the level of fallopian tube insertion. The bulk of the uterine body, but not the cervix, is muscle. The inner surfaces of the anterior and posterior walls lie almost in contact, and the cavity between these walls forms a mere slit. The nulligravid uterus measures 6 to 8cm in length compared with 9 to 10 cm in multiparas. The nongravid uterus averages 60g and typically weighs more in parous women. In nulligravida, the fundus and cervix are approximately equal length, but in multiparas, the cervix is only a little more than a third of the total length. Pregnancy stimulates remarkable uterine growth, which is initially due to muscle fiber hypertrophy. Ater 12 weeks gestation, increasing uterine size is related to pressure exerted by the expanding conceptus. At term, the organ weighs nearly 1100 g. The uterine fundus becomes dome shaped. Moreover, the round ligaments appear to insert at the junction of the middle and upper thirds of the organ. The fallopian tubes elongate, but the ovaries grossly appear unchanged. Almost the entire posterior wall of the uterus is covered by serosa, that is, visceral peritoneum. The lower portion of this same peritoneum forms the anterior boundary of the posterior cul de-sac (rectouterine pouch) or pouch of Douglas. On the anterior wall of the uterus, only the upper portion is covered by peritoneum. The peritoneum of the lower anterior wall reflects forward onto the bladder dome. With this arrangement, the lower anterior uterine wall and cervix are separated from the posterior wall of the bladder by a well-defined loose connective tissue layer-the vesicouterine/vesicocervical space. The uterine wall has three layers:

1. **Endometrium** = inner lining; Site of implantation of the developing embryo. Made up of simple columnar epithelium, stroma of connective tissue and endometrial glands. It has 2 layers; a functional layer: An outer layer that is shed during menstruation; and a basal layer: An inner layer that replaces functional layer after menses.

2. **Myometrium**: Bundles of smooth muscle that form the bulk of the uterus.

3. **Perimetrium**: Serous layer that forms the visceral covering of the uterus.

The Cervix is the lower portion of uterus that connects it to the vagina. anatomical structure**.** Its round outer lower surface (ectocervix) deeps into the upper vagina and is covered by stratified squamous epithelium and has an opening called the external cervical os which

opens into the cervical canal (endocervix), lined by simple cuboidal epithelium. The cervical canal opens into the uterine cavity through the internal cervical os.

The uterus derives its blood supply from both the uterine and ovarian arteries. The uterine artery, a main branch of the internal iliac artery and the ovarian artery a branch of the abdominal aorta.

❖ **Ligaments that support the Uterus**

There are several ligaments that hold the uterus in place within the pelvis.

1. Broad ligament: Attach lateral walls of the uterus to the walls of the pelvis
2. Round Ligament: Fibromuscular bands attached to the uterus on either side in front of and below the opening of the fallopian tubes. It passes through the inguinal canal to the labia majora. It corresponds to the male spermatic cord.
3. Utero-sacral ligament: Links the isthmus of the cervix to the sacrum.
4. Cardinal Ligament (Mackenrodt ligament): Links the uterine cervix and the vault of the lateral fornix of the vagina.

❖ **Fallopian Tubes**

Also called uterine tubes, oviducts, or salpinges, these serpentine tubes extend 8 to 14 cm from the uterine cornua and are anatomically classified along their length as;

-**Interstitial:** portion which is embodied within the uterine muscular wall and opens in the uterine cavity.

-**Isthmus**: narrow portion close to uterus.

-**Ampulla:** more lateral ampulla and large portion of the oviduct where fertilization occurs.

-**Infundibulum:** Funnel shaped end of the ampulla with finger-like processes called fimbriae which opens in the abdominal cavity one of which is attached to the ovary to guide eggs to the oviduct (fimbria ovarica).

The latter three extrauterine portions are covered by the mesosalpinx at the superior margin of the broad ligament. In cross section, the extrauterine fallopian tube contains a mesosalpinx, myosalpinx, and endosalpinx. The tubal musculature undergoes rhythmic contractions constantly, the rate of which varies with cyclical ovarian hormonal changes. The tubal mucosa or endosalpinx is a single layer of columnar epithelium consisting of ciliated,

secretory, and intercalary cells resting on a sparse lamina propria. It is in close contact with the underlying myosalpinx. The current produced by the tubal cilia is such that the direction of fl ow is toward the uterine cavity. Tubal peristalsis created by cilia and muscular layer contraction is believed to be an important factor in ovum transport.

The ovarian artery sends several branches through the mesosalpinx to supply the fallopian tubes, the venous plexus, lymphatic drainage, and nerve supply of the fallopian tubes follow a similar course to that of the ovaries.

❖ **The Ovaries**

The ovaries are generally oval in shape and have a white glistening appearance. They vary in size, position, and appearance, depending on the age and the hormonal status of each woman. During childbearing years, they are generally 2.5 to 5 cm long, 1.5 to 3 cm thick, and 0.6 to 1.5cm wide. Ovaries usually lie in the upper part of the pelvic cavity and rest in a slight depression on the lateral pelvic wall called the ovarian fossa. The medial aspect of the ovary is connected to the uterus by the ovarian ligament, also called the uteroovarian ligament Laterally, each ovary is attached to the pelvic wall by the suspensory ligament, also termed the infundibulopelvic ligament of the ovary, which contains the ovarian vessels and nerves. The ovary consists of;

-**Cortex:** the outermost portion of the cortex is smooth, has a dull white surface, and is designated the tunica albuginea. On its surface, there is a single layer of cuboidal epithelium, the germinal epithelium of Waldeyer. Beneath this epithelium, the cortex contains oocytes and developing follicles.

-**Medulla:** the central portion, which is composed of loose connective tissue. There are numerous arteries and veins in the medulla and a pauciry of smooth muscle fibers. The hilum represents the depression along the mesovarian margin of the ovary where vessels and nerves enter or exit the ovary. The ovaries are supplied by the ovarian arteries, which arise from the anterior surface of the abdominal aorta just below the origin of the renal arteries and from the ovarian branches of the uterine arteries. The ovarian veins follow the same retroperitoneal course as the arteries. However, the right ovarian vein drains into the inferior vena cava, and the left ovarian vein drains into the left renal vein. Lymphatic drainage of the ovaries follows the ovarian vessels to the lower abdominal aorta. Here, lymphatic vessels drain into the paraaortic nodes[24,25].

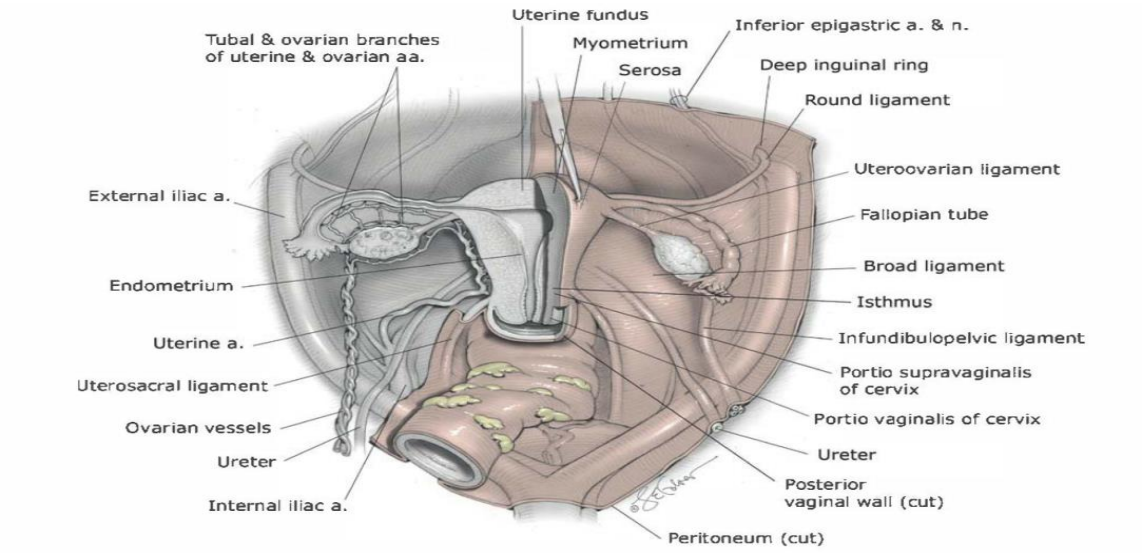

Figure 3 : Uterus adnexa and associated anatomy

(Source Operative Obstetrics: 3rd edition. Cunningham and Gilstrap, page 39)

II.3. PHYSIOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM

II.3.1. Oogenesis

Primordial or primitive follicles appear in the female foetus between the 8th and 10th week of gestation. Near the time of birth, all oocytes in these follicles (primary oocytes) have started and are blocked in prophase of meiosis I. The total number of primary oocytes at birth is estimated to vary from 700,000 to 2 million. During childhood most oocytes die; only approximately 400,000 are present by the beginning of puberty, and fewer than 500 will be ovulated. Oocytes only continue division at puberty during each menstrual cycle. Some oocytes that reach maturity late in life have been dormant in prophase I division for 40 years or more before ovulation. This increases the risk of having children with chromosomal abnormalities like Down's syndrome with advancing maternal age since these oocytes are vulnerable to damage as they age.

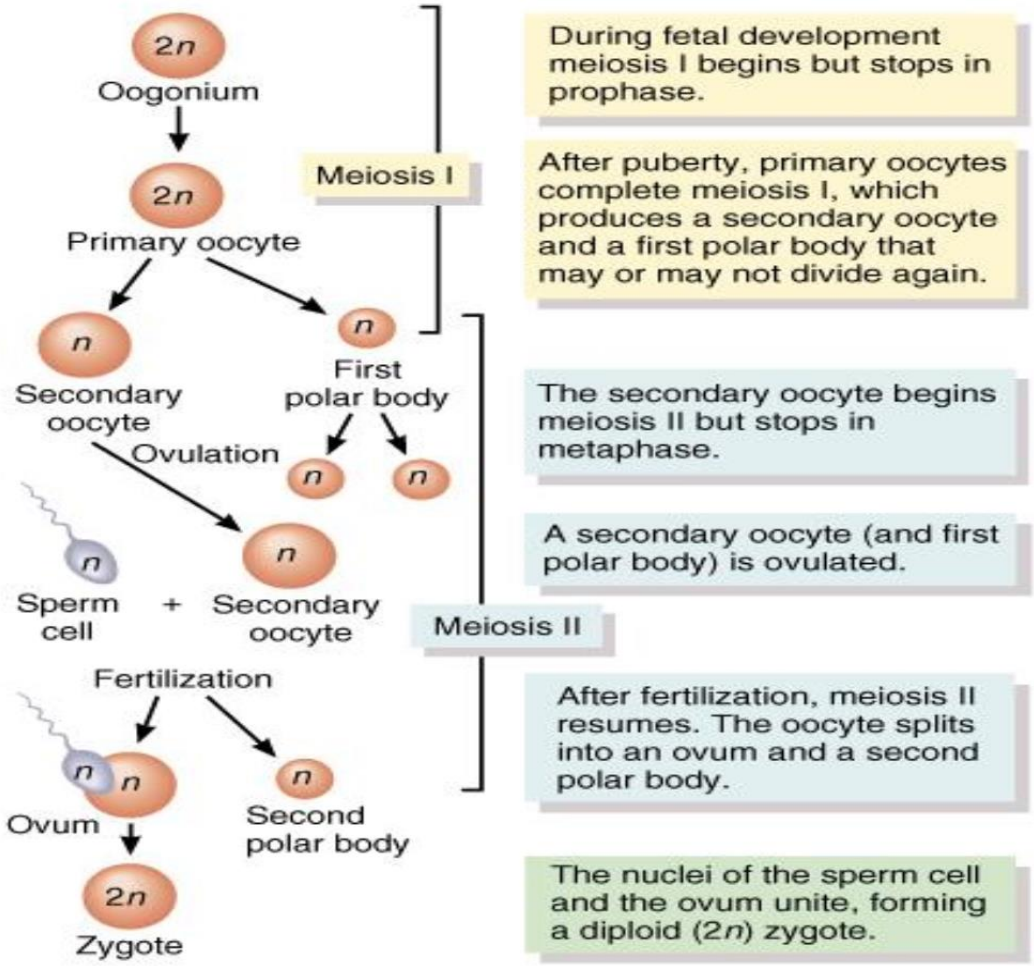

Figure 4 : Stages of oogenesis

(Source: Williams Gynaecology Third Edition. Page 336)

II.3.2. The Menstrual Cycle

Menstruation is the periodic and cyclical shedding of blood and cells from the endometrium. Its onset (menarche) is at the age of 11-14 years. Length of the entire cycle varies between 21 and 35 days (28 ± 7 days) with average duration of bleeding of 3 to 7 days (5±2 days). Blood loss during menses per cycle is about 25-60 ml. The menstrual cycle can be divided into 3 stages which represent changes in reproductive organs that occur simultaneously under the influence of hormones produced in the anterior pituitary gland and the ovary.

Ovarian cycle: At beginning of the cycle, 15 to 20 follicles begin to mature (alternating 2 ovaries), upon stimulation by FSH. Only one (dominant follicle) usually reaches maturity. The stages of growth and maturity are;

- As the primary oocyte in the primordial follicle grows surrounding flat epithelial cells called follicular cells change to cuboidal cells and proliferate to produce a stratified epithelium (Granulosa cells). The follicle becomes known as the primary follicle.
- Granulosa cells rest on a basement membrane separating them from surrounding ovarian (theca folliculi). Cells of the theca folliculi organize into an inner layer of secretory cells (theca interna) that produce androgens, and an outer fibrous capsule (theca externa)
- Granulosa cells convert these androgens to oestrogens
- Granulosa cells and the oocyte secrete a layer of glycoproteins on surface of the oocyte (zona pellucida)
- Fluid-filled spaces appear between granulosa cells.
- Coalescence of these spaces forms the antrum, and the follicle is now termed a secondary (vesicular, Graafian) follicle (20mm in diameter)
- Granulosa cells surrounding the oocyte remain intact and form the cumulus oophorus.
- When the secondary follicle is mature, a surge in luteinizing hormone (LH) induces the preovulatory growth phase.
- Meiosis I is completed, formation of two daughter cells of unequal size, each with 23 chromosomes.
- One cell, the secondary oocyte, receives most of the cytoplasm; the other, the first polar body, receives none.
- The cells then enter meiosis II but arrests in metaphase approximately 3 hours before ovulation.
- Meiosis II is completed only if the oocyte is fertilized; otherwise, the cell degenerates approximately 24 -48 hours after ovulation.
- When oocyte is released, the remains of the follicle are filled with blood to form the Corpus Hemorrhagicum. Some blood can spill into the abdomen and irritate it causing pains known as ovulation pain or **Mittelschmerz**
- With time, blood in the corpus hemorrhagicum is replaced by fatty tissue known as the Corpus luteum. It produces progesterone which helps growth of secretary glands on endometrium in preparation for implantation and maintains pregnancy for the first 3 months before the placenta takes over progesterone production.

If pregnancy occurs, a hormone produced by the developing placenta, hCG maintain the corpus luteum. If pregnancy does not occur, the corpus luteum will degenerate exactly 10 days after ovulation. 4 days later, the endometrium disintegrates and flow out as menses (menses occurs 14 days after ovulation). This 14-day period is called luteal or post ovulatory phase and often associated with a slight increase in temperature. The period from the onset of menses when a new follicle starts developing to ovulation is called the follicular or pre ovulatory phase. It varies in length from person to person. The corpus luteum is replaced by scar tissue called the corpus Albicans (white body).

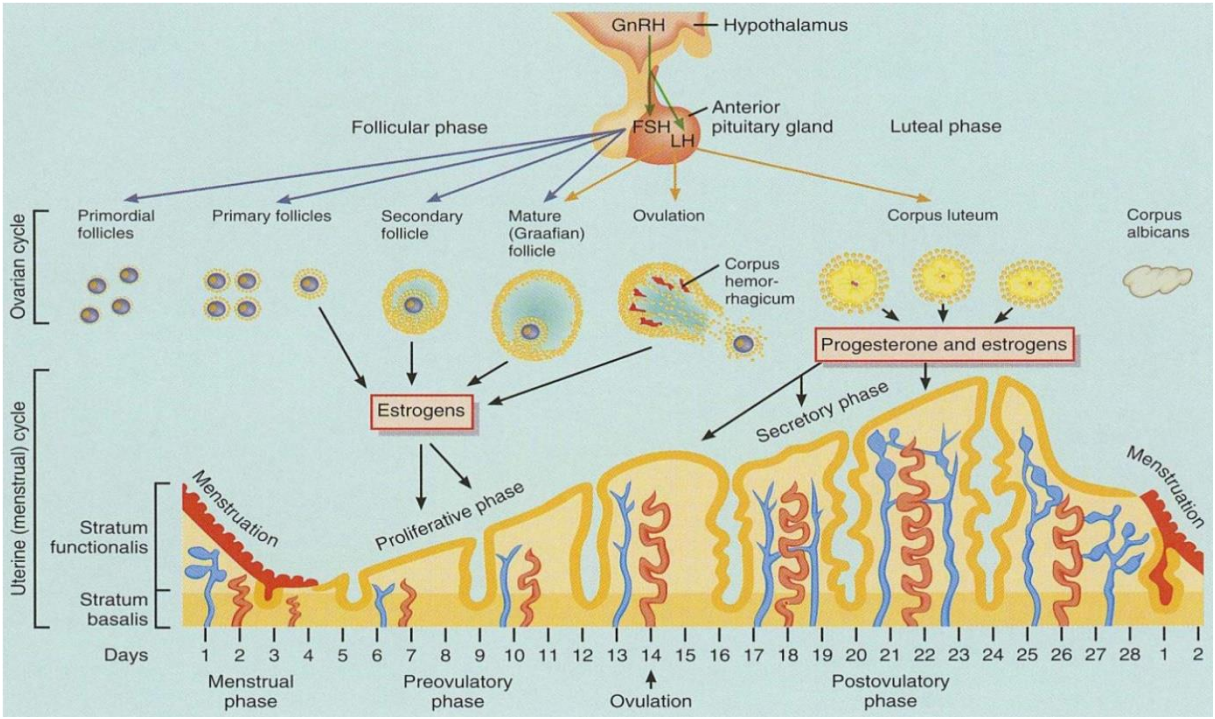

Figure 5 : Hypothalamo-pituitary gonadal axis

(Source: Williams Gynaecology Third Edition. Page 339)

Uterine Cycle: During the follicular phase, oestrogens produced by the follicles stimulate growth of functional layer of endometrium. This is called proliferative phase of endometrium. After ovulation (luteal phase), progesterone produced by corpus luteum causes development of glands in the developed uterine endometrium. These glands produce juicy secretions that will supply nutrients to the developing embryo after implantation. This is called the Secretory phase of the endometrium. If implantation does not occur, progesterone secretion will stop and the endometrium becomes necrotic and filled with blood which flows out as menses. Menstrual blood is 75% arterial and 25% venous blood

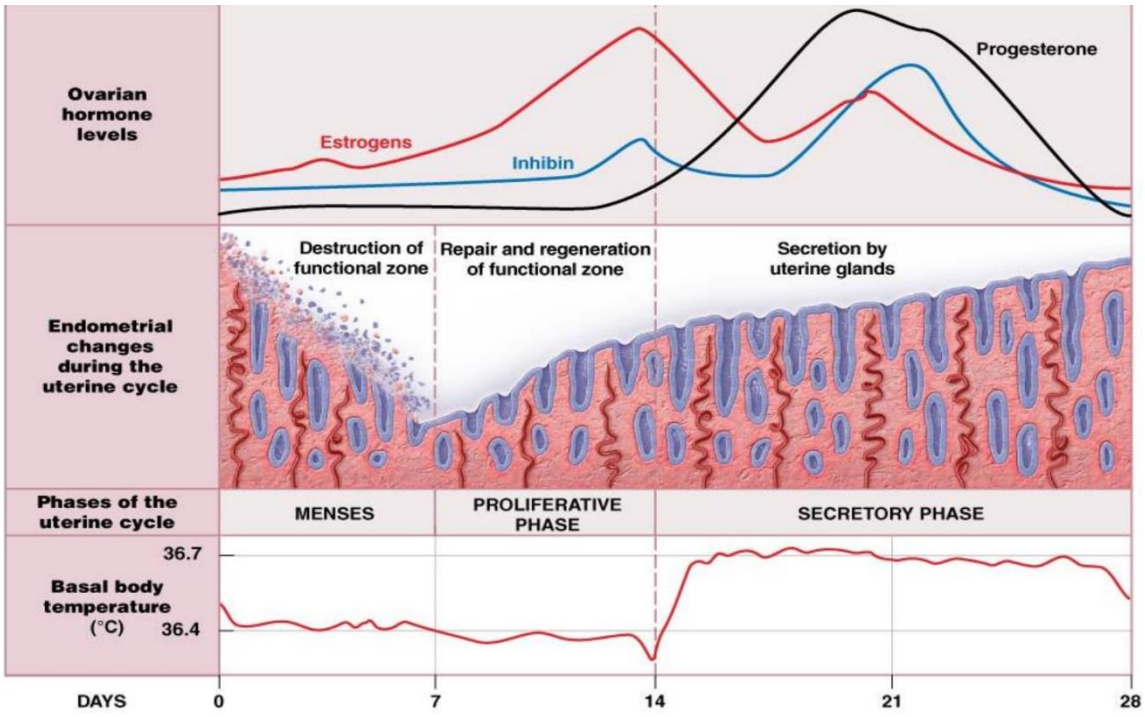

Figure 6 : Stages of ovarian axis

(Source: Williams Gynaecology Third Edition. Page 339)

Cervical Cycle: After menstruation, cervix starts producing mucus secretions which is white, thick and sticky. As oestrogen levels increase during the follicular phase, cervical mucus becomes clear. Around ovulation, it stretchy and transparent like egg-white. This makes it easy for sperms to swim through. After ovulation, under the influence of progesterone, cervical mucus becomes thick again and disappears[26].

II.4. FERTILIZATION AND IMPLANTATION

Fertilization, the process by which male and female gametes fuse, occurs in the ampullary region of the uterine tube. This is the widest part of the tube and is close to the ovary. Spermatozoa may remain viable in the female reproductive tract for several days. Only 1% of sperm deposited in the vagina enter the cervix, where they may survive for many hours. Movement of sperm from the cervix to the uterine tube occurs by muscular contractions of the uterus and uterine tube and very little by their own propulsion. The trip from cervix to oviduct can occur as rapidly as 30 minutes or as slow as 6 days. After reaching the isthmus, sperm become less motile and cease their migration. At ovulation, sperm again become motile, perhaps because of chemoattractants produced by cumulus cells surrounding the egg, and swim to the ampulla, where fertilization usually occurs. Spermatozoa are not able to fertilize the oocyte immediately upon arrival in the

female genital tract but must undergo (1) Capacitation and (2) the acrosome reaction to acquire this capability.

Capacitation is a period of conditioning in the female reproductive tract that in the human lasts approximately 7 hours. Thus, speeding to the ampulla is not an advantage, since capacitation has not yet occurred and such sperm are not capable of fertilizing the egg. Much of this conditioning during capacitation occurs in the uterine tube and involves epithelial interactions between the sperm and the mucosal surface of the tube. During this time, a glycoprotein coat and seminal plasma proteins are removed from the plasma membrane that overlies the acrosomal region of the spermatozoa. Only capacitated sperm can pass through the corona cells and undergo the acrosome reaction.

Acrosome reaction, which occurs after binding to the zona pellucida, is induced by zona proteins. This reaction culminates in the release of enzymes needed to penetrate the zona pellucida, including acrosin- and trypsin-like substances.

The phases of fertilization include;

- Phase 1, penetration of the corona radiate
- Phase 2, penetration of the zona pellucida
- Phase 3, fusion of the oocyte and sperm cell membranes

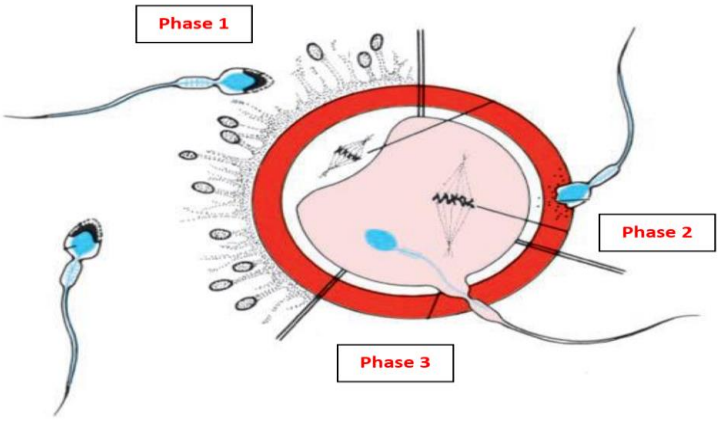

Figure 7 : stages of fertilisation

(Source: Langman's Medical Embryology, 12th edition page 33)

❖ **Phase 1: Penetration of the Corona Radiata**

Of the 200 to 300 million spermatozoa normally deposited in the female genital tract, only 300 to 500 reach the site of fertilization. Only one fertilizes the egg. It is thought that the others

aid the fertilizing sperm to penetrate the barriers that protect the female gamete. Capacitated sperm pass freely through corona cells.

❖ **Phase 2: Penetration of the Zona Pellucida**

The zona is a glycoprotein shell surrounding the egg that facilitates and maintains sperm binding and induces the acrosome reaction. Both binding and the acrosome reaction are mediated by the ligand ZP3, a zona protein. Release of acrosomal enzymes (acrosin) allows sperm to penetrate the zona, thereby coming in contact with the plasma membrane of the oocyte. Permeability of the zona pellucida changes when the head of the sperm comes in contact with the oocyte surface. This contact results in release of lysosomal enzymes from cortical granules lining the plasma membrane of the oocyte. In turn, these enzymes alter properties of the zona pellucida (zona reaction) to prevent sperm penetration and inactivate species- specific receptor sites for spermatozoa on the zona surface. Other spermatozoa have been found embedded in the zona pellucida, but only one seems to be able to penetrate the oocyte.

❖ **Phase 3: Fusion of the Oocyte and Sperm Cell Membranes**

The initial adhesion of sperm to the oocyte is mediated in part by the interaction of integrins on the oocyte and their ligands, disintegrins, on sperm. After adhesion, the plasma membranes of the sperm and egg fuse. Because the plasma membrane covering the acrosomal head cap disappears during the acrosome reaction, actual fusion is accomplished between the oocyte membrane and the membrane that covers the posterior region of the sperm head. In the human, both the head and the tail of the spermatozoon enter the cytoplasm of the oocyte, but the plasma membrane is left behind on the ooocyte surface. As soon as the spermatozoid enters the oocyte, the egg responds in three ways.

1. Cortical and zona reactions. As a result of the release of cortical oocyte granules, which contain lysosomal enzymes, (a) the oocyte membrane becomes impenetrable to other spermatozoa, and (b) the zona pellucida alters its structure and composition to prevent sperm binding and penetration. These reactions prevent polyspermy (penetration of more than one spermatozoon into the oocyte).

2. Resumption of the second meiotic division. The oocyte finishes its second meiotic division immediately after entry of the spermatozoid. One daughter cell, which receives hardly any cytoplasm, is known as the second polar body; the other cell is the definitive oocyte. Its chromosomes (22+X) arrange themselves in a vesicular nucleus known as the female pronucleus.

3. Metabolic activation of the egg. The activating factor is probably carried by the spermatozoon. Postfusion activation may be considered to encompass the initial cellular and molecular events that are associated with early embryogenesis.

The main results of fertilization are as follows:

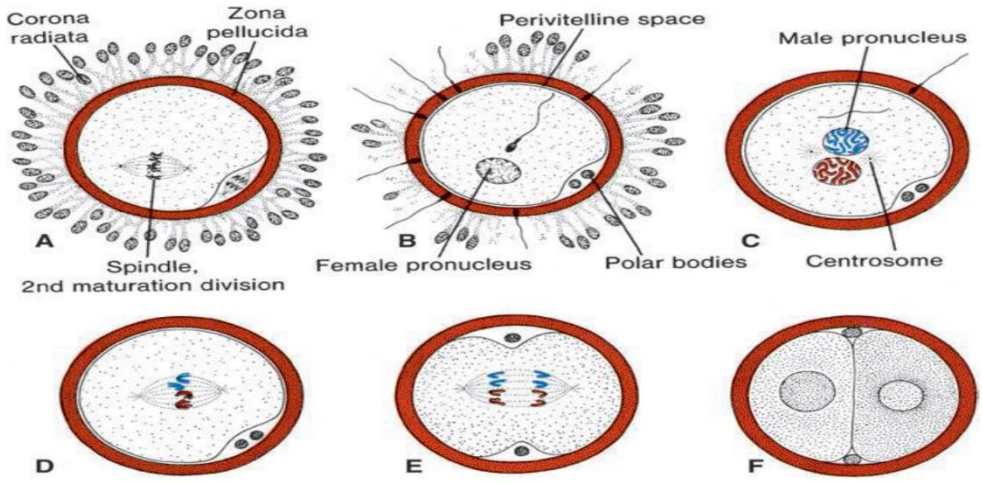

Figure 8 : Fertilisation and zygote formation

(Source: Langman's Medical Embryology, 12th edition page 34)

The main results of fertilization are as follows:

1. Restoration of the diploid number of chromosomes, half from the father and half from the mother. Hence, the zygote contains a new combination of chromosomes different from both parents.

2. Determination of the sex of the new individual. An X-carrying sperm produces a female (XX) embryo, and a Y-carrying sperm produces a male (XY) embryo. Therefore, the chromosomal sex of the embryo is determined at fertilization.

3. **Initiation of cleavage.** Without fertilization, the oocyte usually degenerates 24 hours after ovulation.

❖ **Cleavage**

Once the zygote has reached the two-cell stage, it undergoes a series of mitotic divisions, increasing the numbers of cells. These cells, which become smaller with each cleavage division, are known as blastomeres. Until the eight-cell stage, they form a loosely arranged clump. After the third cleavage, however, blastomeres maximize their contact with each other, forming a compact ball of cells held together by tight junctions. This process, compaction, segregates inner cells, which communicate extensively by gap junctions, from outer cells. Approximately 3 days after

fertilization, cells of the compacted embryo divide again to form a 16-cell morula (mulberry). Inner cells of the morula constitute the inner cell mass, and surrounding cells compose the outer cell mass. The inner cell mass gives rise to tissues of the embryo proper, and the outer cell mass forms the trophoblast, which later contributes to the placenta.

The two-cell stage is reached approximately 30 hours after fertilization; the four-cell stage is reached at approximately 40 hours; the 12- to 16-cell stage is reached at approximately 3 days; and the late morula stage is reached at approximately 4 days. During this period, blastomeres are surrounded by the zona pellucida, which disappears at the end of the fourth day.

❖ **Blastocyst formation and implantation**

About the time the morula enters the uterine cavity, fluid begins to penetrate through the zona pellucida into the intercellular spaces of the inner cell mass. Gradually, the intercellular spaces become confluent, and finally, a single cavity, the blastocele forms. At this time, the embryo is a blastocyst. Cells of the inner cell mass, now called the embryoblast, are at one pole, and those of the outer cell mass, or trophoblast, flatten and form the epithelial wall of the blastocyst. The zona pellucida has disappeared, allowing implantation to begin. In the human, trophoblastic cells over the embryoblast pole begin to penetrate between the epithelial cells of the uterine mucosa on about the sixth day. New studies suggest that L selectin on trophoblast cells and its carbohydrate receptors on the uterine epithelium mediate initial attachment of the blastocyst to the uterus. Selectins are carbohydrate-binding proteins involved in interactions between leukocytes and endothelial cells that allow leukocyte “capture” from flowing blood. A similar mechanism is now proposed for “capture” of the blastocyst from the uterine cavity by the uterine epithelium. Following capture by selectins, further attachment and invasion by the trophoblast involve integrins, expressed by the trophoblast and the extracellular matrix molecules laminin and fibronectin. Integrin receptors for laminin promote attachment, while those for fibronectin stimulate migration. These molecules also interact along signal transduction pathways to regulate trophoblast differentiation, so that implantation is the result of mutual trophoblastic and endometrial action. Hence, by the end of the first week, the human embryo has passed through the morula and blastocyst stages and has begun implantation in the uterine mucosa[27].

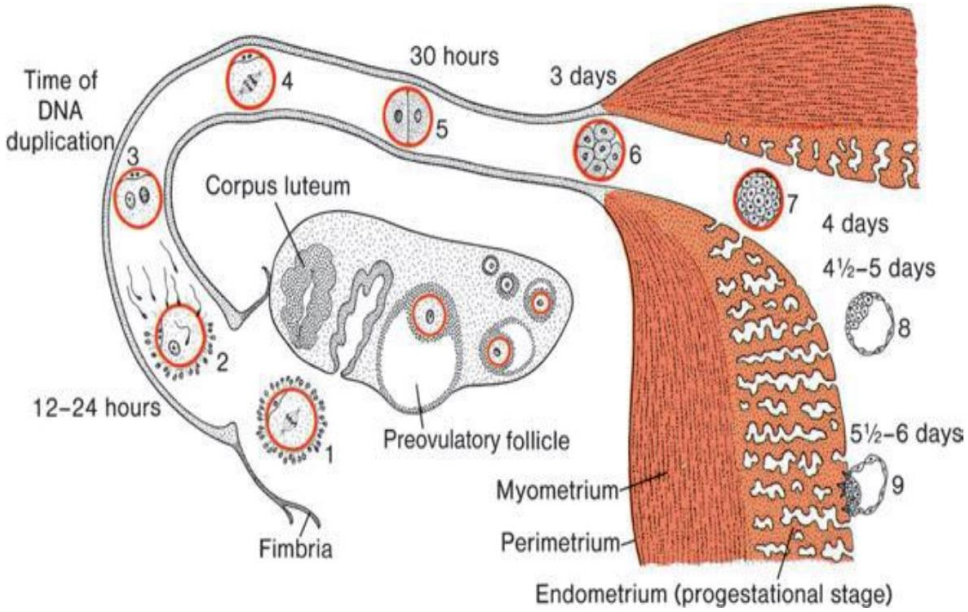

Figure 9 : Events during first week of human development

(Source: Langman's Medical Embryology, 12th edition page 34)

II.5. PATHOGENESIS OF ECTOPIC PREGNANCY

II.5.1. Pathophysiology

Our understanding of the pathophysiology of EP is limited. Current literature supports the hypothesis that the major cause of ectopic implantation is malfunction of the tube itself, although embryonic and uterine factors may also be implicated. Tubal malfunction results from alterations in tubal transport mechanisms and expression of molecules that normally inhibit blastocyst implantation in the Fallopian tube[28].

Anatomic distortion and obstruction of the fallopian tube are widely believed to be responsible for most ectopic implantations. Obstruction could result from PID, salpingitis isthmica nodosa, tubal endometriosis, or postsurgical fibrosis. Scarring of the endosalpinx could lead to diverticuli formation, in which the zygote could be trapped, or to simple obstruction of the tubal passage[20] hence preventing progress of the zygote.

Tubal motility seems to be influenced by the hormonal milieu. The suspicion that some cases of ectopic pregnancy may be due to endocrine abnormalities stems from clinical observations that have suggested an association in patients using a progesterone-only pill, an IUD, or human menopausal gonadotropins for ovulation induction[29]. Transport of the embryo through the Fallopian tube is controlled by smooth muscle contraction and ciliary beating. Inflammation within

the Fallopian tube, resulting from infection or smoking, appears to affect embryo-tubal transport by disrupting smooth muscle contractility and ciliary beat activity[22].

An abnormal conceptus could theoretically result in defective migration of premature implantation in an ectopic site. This possibility has been investigated by examining the chromosomal constitution of ectopic gestations with chromosomal anomalies marked in the elderly[20].

In transperitoneal migration, a fertilized or nonfertilized ovum is transferred to the opposite tube via the peritoneal fluid. Similarly, spermatozoa that have gained access to the peritoneal cavity via a patent oviduct may enter the opposite tube, which is proximally occluded but distally open[30].

Implantation requires regulated local expression of pro- and anti-inflammatory cytokines, chemokines, adhesion molecules, and angiogenic factors. Implantation also involves a series of events, including a change from an initial pro-inflammatory environment to an anti-inflammatory environment. Chemokines play important roles in homing of leukocytes to specific regions within a tissue and activation of leukocytes. This is believed to create a local microenvironment permissive to implantation, tissue remodelling, and embryo development. It is speculated that the inflammatory response of the uterine horn or tube has an effect on the intrauterine environment, which may encourage the embryo to implant in the interstitial segment. Aseptic inflammation associated with electrocoagulation-induced injury at the fallopian tube stump or uterine horn produces chemokines, which may cause embryonic migration to and implantation in the uterine horn. This may explain the increased IP rate in patients with previous salpingectomy[14].

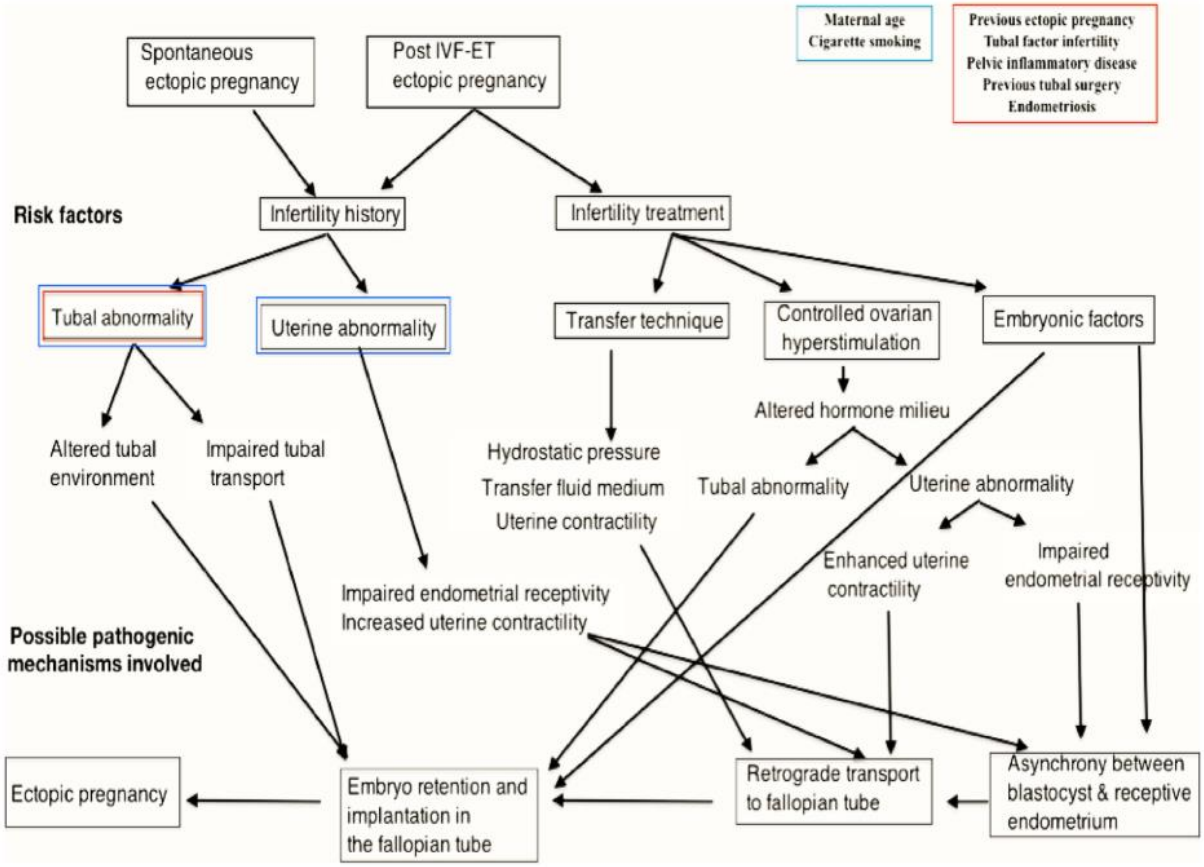

Figure 10 : Pathogenic mechanism of ectopic pregnancy

Source; Ectopic pregnancy secondary to in vitro fertilisation-embryo transfer: pathogenic mechanisms and management strategies[20].

II.5.2. Anatomical sites

The great majority of ectopic pregnancies implant in the fallopian tube 96-98% with about 80% ampullary. Cornual/interstitial 2-5%, Cervical <1%, ovarian 1-2% and abdominal <1%.

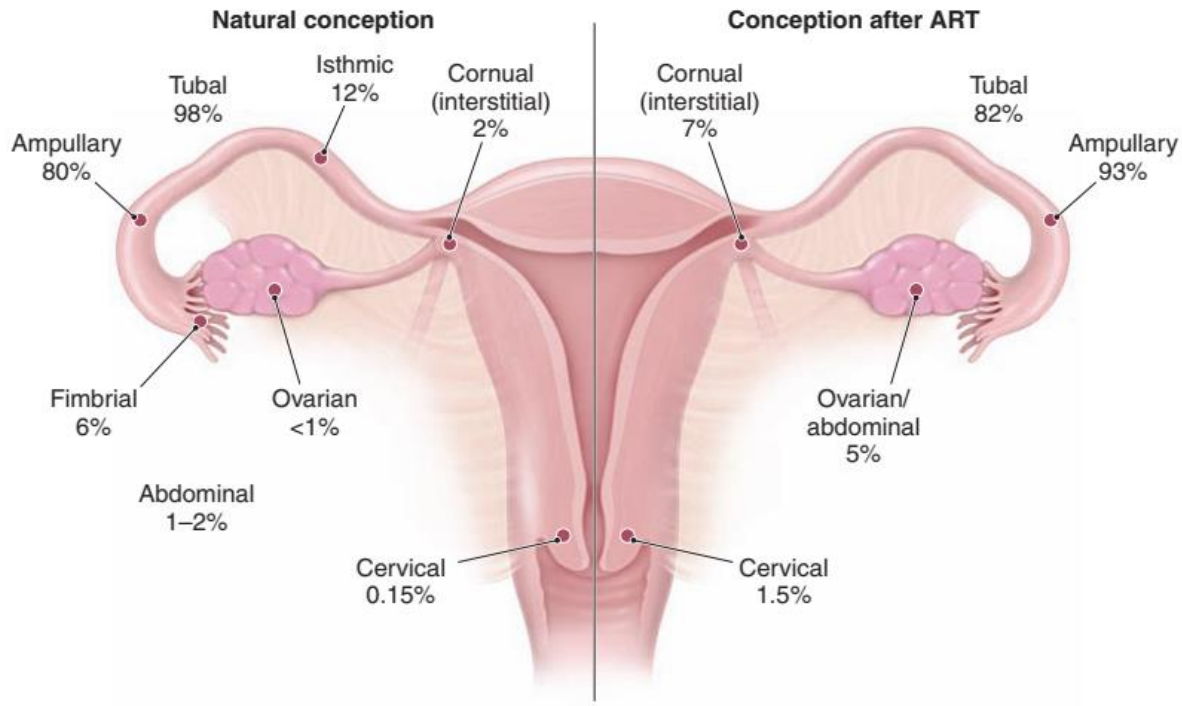

Figure 11 : Incidence of types of ectopic pregnancy by location

(Source: *Obstetrics and Gynecology;* 6th edition Charles R. B. Beckmann page 142)

1. Tubal pregnancy: Several factors may be involved in the pathogenesis of tubal pregnancies, but they are generally believed to be the result of conditions that delay or prevent passage of the fertilized oocyte into the uterine cavity or factors inherent in the embryo that result in premature implantation.

2. Interstitial: The interstitial portion of the fallopian tube is the proximal segment that is embedded within the muscular wall of the uterus. A pregnancy implanted at this site is called an interstitial pregnancy at times cornual. A clue to correct diagnosis is its eccentric location and thin (less than 5 mm) myometrial mantle.

3. Rudimentary uterine horn pregnancy: A rudimentary horn pregnancy is an intrauterine pregnancy that is located in the rudimentary uterine horn of a unicornuate uterus. The term "cornual pregnancy" was originally used to refer exclusively to either this location of a gestation or one located in the horn of a bicornuate uterus, as noted above. However, such pregnancies have a high risk of uterine rupture.

4. Angular or corneal pregnancy: Angular pregnancy is an intrauterine pregnancy with a clinical course distinct from interstitial pregnancy. The pregnancy is implanted medial to the uterotubal junction in the lateral angle of the uterine cavity, close to the proximal ostium of the fallopian tube. In contrast with an interstitial pregnancy, an angular pregnancy is located medial

to the round ligament. When viewed from the exterior of the uterus during laparoscopy or laparotomy, the uterine enlargement caused by an angular pregnancy displaces the round ligament superiorly and laterally, while remaining medial to the ligament itself. On the other hand, an interstitial pregnancy causes an enlargement of the uterus that is lateral to the round ligament. Angular pregnancy appears to be rare, and there are few reports regarding its diagnosis or management. Regardless of the confusion around the terminology for cornual pregnancy, the sonographic criteria for this type of pregnancy are an empty uterine cavity, a gestational sac located eccentrically (1 cm from the lateral wall of the uterine cavity), and a thin myometrial layer (<5 mm) surrounding the gestational sac[31].

The terms cornual, interstitial and angular pregnancies are used inconsistently in the literature. Some authors use interstitial and cornual synonymously, while others reserve cornual for pregnancies in bicornuate or septate uteri. Others distinguish interstitial from angular pregnancy, while in practice many physicians are unfamiliar with the latter designation[32]

Criteria for presumed angular pregnancy

▪ Nonanomalous uterus: not unicornuate, bicornuate, or septate[1]
▪ Implantation of the embryo in the lateral angle of the uterine cavity, just medial to the uterotubal junction[2]
▪ No more than 1 cm of myometrial thickness from the gestational sac to the outer border of the uterus
▪ Presence of completely circumferential endometrium surrounding the gestational sac and, therefore, diagnostic of intrauterine gestation[3]
▪ Lack of an "interstitial line sign"; this is defined as an echogenic line in the upper lateral region of the uterus bordering the gestational sac and is thought to represent the interstitial portion of the fallopian tube[4]

From: Bollig KJ, Schust DJ. Refining Angular Pregnancy Diagnosis in the First Trimester: A Case Series of Expectant Management. Obstet Gynecol 2020; 135:175. DOI: 10.1097/AOG.0000000000003595. Copyright © 2020 the American College of Obstetricians and Gynecologists. Reproduced with permission from Wolters Kluwer Health. Unauthorized reproduction of this material is prohibited.

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4. *Ackerman TE, Levi CS, Dashefsky SM, Holt SC, Lindsay DJ. Interstitial line: sonographic finding in interstitial (cornual) ectopic pregnancy. Radiology 1993; 189:83.*

5. Heterotopic pregnancy: Heterotopic pregnancy refers to the combination of an intrauterine pregnancy and a concurrent pregnancy at an ectopic location.

6. Cervical pregnancy: A cervical pregnancy is a rare form of ectopic pregnancy in which the trophoblast implants in the cervical tissue of the endocervical canal. **Rubin's Histopathologic criteria** for diagnosis of cervical pregnancy include;

i. Cervical glands present opposite to the placenta.

ii. Placental attachment to the cervix must be below the entrance of uterine vessels.

iii. Foetal elements should be absent from the corpus uteri

Rubin's ultrasound criteria for diagnosis of cervical pregnancy include**;**

i. An hourglass uterine shape

ii. Ballooned cervical canal

iii. Gestational tissue at the level of the cervix

iv. Absent intrauterine gestational tissue

v. Portion of the endocervical canal seen interposed between the gestation and endometrial canal

7. Ovarian pregnancy — Ovarian pregnancy occurs in approximately 1 to 3 percent of ectopic pregnancies and is becoming more common. In contrast with tubal pregnancy, a history of pelvic inflammatory disease or the use of an intrauterine contraceptive device does not increase the risk of ovarian pregnancy. Ovarian pregnancy appears to be a random event that is not associated with a history of infertility or recurrent extrauterine pregnancy. Spiegelberg's criteria are used to diagnose a primary ovarian pregnancy

Criteria for diagnosis (Spiegelberg's Criteria)

1. The fallopian tube on the affected side must be intact
2. The fetal sac must occupy the position of the ovary
3. The ovary must be connected to the uterus by the ovarian ligament
4. Ovarian tissue must be located in the sac wall

8. Abdominal pregnancy; may be primary, from direct implantation of the blastocyst on the peritoneal surface or abdominal viscera, or secondary, resulting from extrusion of an embryo from the tube. Studdiford's criteria are used to diagnose a primary abdominal pregnancy

Criteria for diagnosis – Studdiford's Criteria

1. Presence of normal tubes and ovaries with no evidence of recent or past pregnancy
2. No evidence of uteroplacental fistula
3. The presence of a pregnancy related exclusively to the peritoneal surface and early enough to eliminate the possibility of secondary implantation after primary tubal abortion

9. Hysterotomy scar pregnancy: Ectopic pregnancy in a previous hysterotomy (caesarean) scar occurs in approximately 1 in 2000 pregnancies and 6 percent of ectopic pregnancies

among patients with a prior caesarean delivery. It does not appear to be related to the number of caesarean deliveries. The pregnancy is located in the scar outside of the uterine cavity and surrounded by myometrium and connective tissue. Implantation in this location is believed to occur because the embryo migrates through a defect within the scar.

10. Intramural pregnancy: Intramural pregnancy is a rare form of ectopic pregnancy, with fewer than 50 reported cases in the literature; in an intramural pregnancy the gestational tissue is located entirely or partially inside the myometrium. Previous injury to the myometrium (e.g., myomectomy, dilation and curettage) could be the predisposing factor. It has also been described in conjunction with adenomyosis. The diagnosis is usually difficult due to different locations inside the uterus and the varying degrees of uterine involvement. Intramural pregnancy must be distinguished from cervical and caesarean scar pregnancy.

II.6. CLINICAL PRESENTATION

Interstitial and cornual pregnancy remain the most difficult type of ectopic pregnancy to diagnose due to late onset of symptoms and the classic triad of ectopic pregnancy abdominal pain, amenorrhea and vaginal bleeding occurs in <40% of patients. Low sensitivity and specificity of symptoms and imaging due to the site of implantation in the intrauterine portion of fallopian tube and invasion through the uterine wall which makes this pregnancy difficult to differentiate from an intrauterine pregnancy on ultrasound[31]. Meanwhile for CEP, The most common symptom is vaginal bleeding following a period of amenorrhea which is often painless and at times massive bleeding can occur[33]. Both are considered high risk because of diagnosis is usually late with haemorrhagic complications. Early diagnosis require a high index of suspicion as it may be asymptomatic or present with nonspecific symptoms[14]. Clinicians should consider ectopic pregnancy as a diagnosis in any patient of reproductive age with vaginal bleeding and/or abdominal pain who has the following characteristics:

1. Pregnant but does not have a confirmed intrauterine pregnancy.

2. Pregnant and conceived with in-vitro fertilization.

3. Pregnancy status uncertain, particularly if amenorrhea of >4 weeks preceded the current vaginal bleeding.

4. In rare cases, a patient who presents with hemodynamic instability and an acute abdomen that is not explained by another diagnosis.

Clinical manifestations of ectopic pregnancy typically appear six to eight weeks after the last normal menstrual period but may occur later, especially if the pregnancy is at an extrauterine site other than the fallopian tube (7-16 weeks for cornual). Normal pregnancy discomforts (eg, breast tenderness, frequent urination, nausea) are sometimes present. Early pregnancy symptoms may be less common in patients with ectopic pregnancy because progesterone, estradiol, and human chorionic gonadotropin levels may be lower than in normal pregnancy[9].

Vaginal bleeding: The volume and pattern of vaginal bleeding vary, and there is no bleeding pattern that is pathognomonic for ectopic pregnancy. Bleeding may range from scant brown staining to haemorrhage. Bleeding is usually intermittent but may occur as a single episode or continuously. The vaginal bleeding associated with ectopic pregnancy is typically preceded by amenorrhea. However, some patients may misinterpret bleeding as normal menses and may not realize they are pregnant prior to developing symptoms associated with ectopic pregnancy. This is particularly true in patients who have irregular menses or who do not keep track of menstrual cycles.

Abdominal pain — The timing, character, and severity of abdominal pain vary, and there is no pain pattern that is pathognomonic for ectopic pregnancy. Pain is usually located in the pelvis and may be diffuse or localized to one side. Pain tends to present between five and seven weeks of gestation as the tube becomes sufficiently distended. Patients may describe their pain as continuous or intermittent, dull or sharp, or mild or severe. Tubal rupture may be associated with an abrupt onset of severe pain. In cases in which there is intraperitoneal blood that reaches the upper abdomen or in rare cases of abdominal pregnancy, the pain may be in the middle or upper abdomen. If there is sufficient intraabdominal bleeding to reach the diaphragm, referred pain may be felt in the shoulder. Blood pooling in the posterior cul-de-sac (pouch of Douglas) may cause an urge to defecate.

II.7. DIAGNOSIS

Symptoms do not differ from tubal EP clinical presentation thus requiring a high index of suspicion. If tubal rupture and subsequent hemoperitoneum have already occurred, patient will present acute abdominal pain and tenderness. Hemodynamic stability can also be compromised if blood loss is consistent. Even women with unruptured pregnancy may also present pelvic pain or vaginal bleeding.

In diagnostic workup of EP, serum dosage of β-human chorionic gonadotropin (β-hCG) is used either for initial diagnosis and follow-up. In the first trimester, for a normal implanted

pregnancy, β-hCG concentration doubles about every 2 days. EP may present rising or stable β-hCG levels. Serial measurement is needed to confirm viability. When an abnormal increase in β-hCG concentration is evidenced, nonviability is assumed, and more investigations must be done to differentiate a miscarriage from an EP. When a pregnancy cannot be found inside the uterus in a patient with b-hCG values higher than 2000 mIU/mL, physician must consider this situation very suspicious of EP until surely excluded. Based on a review of β-hCG levels with known pregnancy locations, a level of 1500 IU/ml has been proposed as the appropriate with trans-vaginal ultrasound. The predictive value of β-hCG rise has been studied: a rise of <67% predicts abnormal pregnancy with 95% certainty, while a rise of <53% give 99% of certainty[34].

Early and accurate diagnosis of IP is possible because of application of high-resolution transvaginal ultrasound (TVUS). With recent advances, IP is diagnosed at a gestational age of 6.9 to 8.2 weeks[14]. In initial pregnancy work up, “double sac sign” is used to document the intrauterine location of pregnancy. Early gestational sac, indeed, implanting into the uterine cavity, appears surrounded by two concentric rings representing the normal decidual reaction surrounding chorionic ring. This sign is fundamental for differentiation of eccentric intrauterine from interstitial EP. At Ultrasound examination cornual pregnancy shows “interstitial line sign” an echogenic line between the eccentrically located gestational sac and endometrial cavity. Furthermore, gestational chamber appears surrounded by myometrium[34].

If the location is not clear or if the infiltration of neighbouring organs is suspected, magnetic resonance imaging can be considered. This is helpful, especially in caesarean scar pregnancy (CSP), to analyse the thickness of the remaining uterus wall after C-section[35].

The diagnosis of ectopic pregnancy can be confirmed when any of the following are present:

- Visualization of an extrauterine gestational sac with a yolk sac or embryo (with or without a heartbeat) on TVUS.
- A positive serum hCG and no products of conception on uterine aspiration with subsequent rising or plateauing hCG levels.
- Visualization at surgery (usually performed for patients with hemodynamic instability) with histologic confirmation following resection of ectopic pregnancy tissue.

❖ **Differential diagnosis**

The classic findings of ectopic pregnancy are vaginal bleeding and/or abdominal pain in the setting of a positive pregnancy test. The differential diagnosis of bleeding with or without pain early in pregnancy also includes

1. Physiologic (e.g., implantation bleeding)

2. Spontaneous abortion

3. Cervical, vaginal, or uterine pathology (e.g., cervical polyp)

4. Subchorionic hematoma

5. Gestational trophoblastic disease (human chorionic gonadotropin concentration is unusually high for the gestational age)

The differential diagnosis of lower abdominal pain in pregnant patients includes;

1. Urinary tract infection

2. Kidney stones

3. Diverticulitis

4. Appendicitis

5. Ovarian pathologies (Ovarian neoplasms, ovarian cyst rupture, large size or haemorrhage into an ovarian cyst, ovarian torsion)

6. Leiomyomas (torsion or aseptic necrobiosis)

7. Round ligament pain.

❖ **Natural history**

If left untreated, an ectopic pregnancy can progress to a tubal abortion or tubal rupture, or it may regress spontaneously.

1. **Tubal rupture** – Tubal rupture is usually associated with profound haemorrhage, which can be fatal if surgery is not performed expeditiously to remove the ectopic gestation which can occur as late as 18 weeks of gestation or even more[36].

2. **Tubal abortion** – Tubal abortion refers to expulsion of the products of conception through the fimbria. This can be followed by resorption of the tissue or by reimplantation of the trophoblasts in the abdominal cavity (i.e., abdominal pregnancy) or on the ovary (i.e., ovarian pregnancy). Tubal abortion may be accompanied by severe intraabdominal bleeding,

necessitating surgical intervention, or by minimal bleeding, which would not require further treatment.

3. **Spontaneous resolution** – this can occur, although it is difficult to predict which patients will experience uncomplicated spontaneous resolution. In rare instances, gestational products left in the fallopian tube can cause tubal obstruction.

II.8. MANAGEMENT OF ECTOPIC PREGNANCY

All-types of ectopic pregnancy can end in potentially life-threatening complications. However, non-tubal ectopic pregnancies represent a particular diagnostic and therapeutic challenge and are at a higher risk of complications with increased morbidity and mortality. There are currently no recommendations concerning CSP, cervical, or cornual pregnancy[35]. Treatment modalities could be pharmacological or surgical, generally, treatment plans should be specific to the patient considering the obstetric history of the patient, the gestational age of the ectopic pregnancy at time of diagnosis and the need for preservation of fertility[9]. Due to good outcomes and fewer risks, in current practice conservative medical and surgical methods of management are preferred. Even though these methods do not protect against recurrence[37].

Table I: Management option for interstitial or cornual ectopic pregnancy

Medical Management	Surgical Management
Ideal indications:	Indications:
- Hemodynamically stable patient	- Hemodynamic instability
- Patient is reliable to adhere to follow-up appointments	- Physical exam: peritoneal signs present
- Sonography: no fetal cardiac activity; gestational sac <3.5 cm in diameter; unruptured mass	- Sonography: fetal cardiac activity; substantial ascites; ruptured mass
- Beta-hCG levels <5000 mIU/mL	- Patient preference or suspected poor patient compliance
- No significant comorbidities or contraindications to methotrexate (e.g., active pulmonary disease, active peptic ulcer diseae, breastfeeding, intrauterine gestational sac, thrombocytopenia, immunodeficiency, hepatic disease, renal disease, leukopenia)	- Significantly elevated beta-hCG levels - Failure of conservative treatment - Significant comorbidities or contraindications to medical management with methotrexate

Source; Interstitial and Cornual Ectopic Pregnancy: A Review of the management Options[9].

❖ **Pharmacological treatment**

This treatment options include systemic or local administration of methotrexate (MTX), chloride potassium, hyperosmolar glucose solution, prostaglandin, or a combination of the medications. The drugs are administered with laparoscopic assistance or are injected directly into

the gestational sac under transabdominal or transvaginal ultrasound control. Ultrasound guided procedure has proven to be effective and with lesser complications than surgery when done on time[38]The dosing for intra-amnial injection is 1 mg/kg body weight, also using a multidose scheme. In the single-dose scheme, 50 mg/m2 is applied intramuscularly to the patient.

Requirement of it is that an appropriate intrauterine pregnancy is excluded, or when surgical treatment in abortion cannot be performed. Relative contraindications need to be considered such as βHCG > 4000, detection of an embryonic heartbeat, lactation, heterotopic pregnancy, maternal comorbidities, allergies, missing compliance of the patient, renal insufficiency, moderate to severe anaemia, leukopenia, or thrombocytopenia, liver disease or alcoholism and active peptic ulcer disease. In higher βHCG levels or with positive heartbeat, the rate of successful MTX treatment is decreasing. In Addition, before treatment, a complete blood count and a comprehensive metabolic panel should be checked.

Common side effects of MTX treatment must be considered like alopecia and elevated liver enzymes. During MTX treatment, patients should be informed to take folic acid supplement. Nonsteroidal anti-inflammatory drugs and sun exposure should be avoided. Patients should receive counselling on the importance of refraining from becoming pregnant for a minimum of 3 months following their treatment. However, patients should be well counselled that this conservative medical management has a relatively high failure rate with past reports showing a failure rate ranging from 9% to 65% and an operation may still be necessary if there is rupture of the ectopic pregnancy[9,35].

Another strategy for conservative treatment involves uterine artery embolization (UAE) under fluoroscopic guidance with or without the use of methotrexate. However, this treatment protocol remains experimental until more studies can be conducted regarding its safety and efficacy in the treatment of interstitial ectopic pregnancies. Furthermore, there have been some cases where women treated with uterine artery embolization experienced endometrial atrophy and infertility (4,9).

❖ **Surgical treatment**

Immediate surgical intervention should be conducted if the patient exhibits serious signs and symptoms of a ruptured ectopic pregnancy. This may include hysterectomy, wedge resection or partial cornual resection by laparotomy or laparoscopy. But increasingly, more conservative approaches are being used such as cornuostomy instead of cornual resection, as well as laparoscopy in place of laparotomy[39,40]. In the last few years, the use of more conservative surgical alternatives, such as cornuostomy rather than cornuectomy, is introduced to better

preserve uterine integrity for future fertility. Many cases of laparoscopic cornuostomy have been reported in the literature so far, but gestational tissue should be removed as completely as possible to avoid further complications.

Regarding surgical treatment, main concerns are haemorrhage and the need for adequate cornual reconstruction to prevent uterine rupture in future subsequent pregnancy. Integrity of myometrium after conservative treatments is unclear; patients must be counselled carefully about the risk of uterine rupture in subsequent pregnancy. The laparoscopic cornuostomy is a more conservative surgical approach which can better preserve the integrity of the uterus to aid in future fertility. To prevent this severe complication, normal uterine tissue must be preserved, avoiding tissue damage by electrosurgery and by minimal excision of cornual tissue. Suture closure of the cornual defect remains the most appropriate method for the achievement of haemostasis and may also minimize the risk of uterine rupture in subsequent pregnancy. Past studies have presented a wide variety of sutures that may be utilized during the interstitial or corneal pregnancy operation including a square suture to achieve haemostasis by compression, an encircling suture which may act like a tourniquet around the ectopic gestational sac, automatic staplers, and the use of endoloop or stapler devices. During subsequent pregnancies, close antenatal surveillance is necessary to monitor the risk of uterine rupture and decrease the incidence of recurrent cornual or interstitial ectopic pregnancies. Usually, future pregnancies will require caesarean deliveries to reduce the risk of uterine rupture in labour[9,31,41,42]. In our environment laparotomy is still the most used route even though minimally invasive surgery is becoming more and more available and practiced[43].

For cervical ectopic pregnancies, in addition to termination of pregnancy by methotrexate and uterine artery embolization (UAE), other conservative methods exist including; curettage or office hysteroscopy, intracervical balloon placement (tamponade with foley's catheter) and intracervical injection of vasopressin. The main complication just like in other ectopic pregnancies is life threatening bleeding due to abnormal vascularization within the cervix and the impossibility of cervical tissue to seal the cervico-placental vessels by contraction after the evacuation of the placenta which may require a hysterectomy[4,6,33,44].

II.9. SUBSEQUENT PREGNANCY AND OUTCOME

Literature is unclear on fertility and obstetrical outcomes following cornual pregnancy, in some they are not affected whatever the initial treatment[10,45] in others after medical treatment for an interstitial pregnancy, the risk of uterine rupture remains unknown for a future pregnancy but this concern exists for interstitial pregnancies that are treated surgically, warranting close

monitoring of these women during pregnancy and elective caesarean section for delivery [11,12]. Some articles have reported cases of uterine rupture during subsequent pregnancies[11,46], while others described safe delivery without any complication in pregnancy[47–49]. Recurrence of cornual pregnancy has also been reported[37,48].

II.10. PUBLICATIONS ON THE SUBJECT

Table II: Publications on the subject

Objectives	Authors/Years	Country	Study design	Results
To identify the risk factors for ectopic pregnancy (EP) in a population of Cameroonian women	Yvette Audrey Assouni Mindjah, Felix Essiben, Pascal Foumane, Julius Sama Dohbit, Emile Telesphore Mboudou 2018	Cameroon	Case-control study	Of the fifteen identified risk factors, 4 were independently associated with increased odds of EP: prior PID (adjusted odds ratio [AOR] 13.18; 95% CI 6.19–27.42), current use of emergency contraceptive levonorgestrel-only pills (LNG-EC) (AOR 10.15; 95% CI 2.21–46.56), previous use of depot medroxyprogesterone acetate (DMPA) (AOR 3.01; 95% CI 1.04–8.69) and smoking at the time of conception (AOR 2.68; 95% CI 1.12–6.40)
A Review of the Management Options	Evelyn Yang Yung-Liang Liu 2022	Taiwan	Literature review	Interstitial or cornual ectopic pregnancies are a rare form of EP (2% to 4% of all ectopic pregnancies). Mortality rate 6–7 times higher than other EPs. Treatment options include conservative medical management with methotrexate or surgical with laparoscopy or laparotomy.
To analyze the characteristics and peculiarity of non-tubal ectopic (NTE) pregnancy	Aderemi Alalade, Kate Mayers, Gani Abdulrahman Jr, Reeba Oliver & Funlayo Odejinmi 2003 to 2014	London, UK	Comparative	The 31–40-year age group and primigravida had the highest incidence (55% and 37%) respectively. Significant associated factors for NTEP were; history of ART (p=0.041) and PID (in cornual pregnancy only). Compared with tubal ectopic pregnancy, NTEP was more likely to present at 6–10 weeks gestational age or later (p=0.000), and more likely to present with shoulder-tip pain and syncopal attack link with significant amount of haemoperitoneum.
To investigate unusual ectopic	Nan Shan, Dan Dong, Weiguo	China	Retrospective comparative	Extratubal EP have a high rate of misdiagnosis and presented more serious manifestations. Some

pregnancies (EP) and compare them with fallopian ones.	Deng and Yan Fu 2000 to 2010			unusual EP could be diagnosed by ultrasonography. Most of the unusual EP underwent surgery, except some early cervical and corneal pregnancies. PID showed particularly significant differences among ovarian ($P < 0.01$), cornual ($P < 0.01$) and tubal pregnancies. Placement of IUD was significantly associated with ovarian pregnancy ($P < 0.01$) in comparison with other unusual EP.
To examine the current state of prevention, risk factors, diagnosis, and management of Interstitial Pregnncy (IP), based on the current literature	Jianmin Chen, Dong Huang, Libing Shi and Songying Zhang 2018	China	Literature review PubMed English language articles	Ipsilateral salpingectomy is the main high-risk factor of IP, especially after in vitro fertilization. Cornual suture at the time of salpingectomy helps to reduce the IP rate. Laparoscopic cornuostomy appears to be an effective treatment in intact cases
Cornual Pregnancy (CP)	Gaetani M, Di Gennaro D, Vimercati A, Vitagliano A, Dellino M, Malvasi A, *et al*. 2023	Italy	Literature review article	Widely recognized risk factors for CP are endometriosis, fibroids, PID. The incidence of uterine ruptures in the scarred uterus appears to be low, but the fear of it remains therefore, medical treatment might be favoured over cornual wedge resection
Cervical ectopic pregnancy	Sunil Kumar Samal, Setu Rathod 2015	India	Case report	Cervical pregnancy <1% of all EPs. Early diagnosis and medical management with systemic or local use of methotrexate is treatment of choice. Dilation and curettage with intracervical Foleys' ballon tamponade, hysteroscopy and total hysterectomy are other options
A Case of Live Birth after Uterine Reconstruction for Recurrent	Deivanayagam Maruthini and Vinay Sharma 2013	*Leeds, UK*	Case report	A case of recurrent ruptured right cornual ectopic pregnancies with cornua reconstruction and thickened in several layers. A further cycle of IVF resulted

Cornual Ectopic Pregnancy following IVF Treatment				in a singleton intrauterine pregnancy. No myometrial thinning in pregnancy. She was delivered by an uneventful elective caesarean section at term
A Live Birth After Laparoscopic Cornual Resection For Cornual Heterotopic Pregnancy After Ivf	Se Jin Lee, Jeong Min Eom, A Ra Koh, Sue Yeon Park, Jung Hun Lee, Joong Sub Choi and Chang Young Hur	Seoul, Korea		A 28-year-old Korean woman with a history of bilateral salpingectomy due to two prior tubal pregnancies conceived a heterotopic cornual pregnancy post-IVF. An emergency laparoscopic right cornual resection was done at the 7th gestational week. The subsequent antenatal course was unremarkable. There were no obstetric or surgery-related complications. The patient delivered a healthy baby of 3,340g via Cesarean section due to failure to progress at term.
To present our experience of laparoscopic management of cornual ectopic pregnancy	Selma Ng, Suttha Hamontri, Irene Chua, Bernard Chern and Anthony Siow 2009	Singapore	Retrospective review of 53 cases	52 cases were managed by laparoscopy, and 1 was converted to laparotomy. Laparoscopic wedge resection was done in 33 patients, cornuostomy in 13 patients, and salpingectomy in 7 patients. Eighteen patients became pregnant, 4 had early miscarriages, and 10 had pregnancies beyond 24 weeks gestation. 5 delivered vaginally, and 3 had cesarean section at term. Two patients traveled back to their native countries for delivery. There were no cases of uterine rupture or dehiscence reported
Uterine rupture in third trimester of pregnancy following cornual resection due to ectopic pregnancy	Vesna Košec, Marijo Čukelj, Ivka Djaković and Dražan Butorac 2021	Croatia	Case report	a case of uterine rupture in the early third trimester in a woman who had undergone previous laparoscopic removal of the left fallopian tube due to sactosalpinx and laparotomy removal of left uterine horn due to ectopic pregnancy

Given the high morbidity and mortality associated with IUEP related to late diagnosis, increased awareness and knowledge on its associated factors could help by providing better prediction and prevention in women at risk. This could also enable an early and accurate diagnosis prior to the rupture, resulting in a reduction in the need for surgery and other complications.

CHAPTER III : METHODOLOGY

III.1. STUDY DESIGN

The study was a hospital-based case-control study.

III.2. STUDY AREA AND SETTING

This study was carried out in 2 hospitals namely, the Yaounde Gynaeco-Obstetric and Paediatric Hospital (YGOPH) and the Yaounde Central Hospital (YCH).

The YGOPH is located in Ngousso, and found at the tertiary level in the Cameroon health system thus one of the highest referral centres in Yaounde and the country. It was constructed as a result of the Sino-Cameroon cooperation to improve maternal, neonatal and child health services in Cameroon. The Gynaeco-obstetric unit has three parts: the maternity ward, the inpatient wards and the outpatient sub-unit. It has a team of 10 Obstetricians-Gynaecologist (including one Professor and two Associate Professors of obstetrics and gynaecology); Residents and interns in obstetrics and gynaecology; Midwifes; Nurses; Medical and Nursing students. The intensive care unit is also made up of a team of 4 (four) Anaesthesiologist-Reanimators including: 1 professor, 3 Specialists, Residents and interns; Nurses; Medical and Nursing students. The Imaging section of the hospital is well equipped with qualified staff. It has a computed tomography (CT) Scan, Ultrasound machines, X-RAY machines and printers. The laboratory is also well equipped with sufficient machines and qualified staff to carry out any investigations with the right interpretations, it is also attached to a blood bank that works 24 hours on 24 and every day. The theatre unit is made up of 4 operating rooms, which are well equipped. This hospital has both the qualified personnel and the equipment to take care of patients with ectopic pregnancy and its complications.

The YCH, created in 1933, it has undergone several structural changes from a day hospital to one of the most utilized hospitals in Cameroon. Located at Massa at the centre of Yaounde city. It is a Second Category hospital which offers to patients a complete medical and paramedical team. It has six specialized units, including the Obstetrics and Gynaecology Unit, also known as the Yaounde Principal Maternity. The Maternity has an outpatient department, emergency unit, delivery room, two operating theatres, a reanimation unit and inpatient service. The Obstetrics and Gynaecology unit has 7 Obstetrician-Gynaecologists; Residents and interns in obstetrics and gynaecology; Nurses; Midwifes; Medical and Nursing students. The blood bank of the YCH is one of the biggest in Cameroon and works 24 hours a day.

These two hospitals have the advantage over other hospitals at the same level in the health system that they receive and take care of patients of all social levels, such that they represent the main referral facilities for health facilities at lower levels of care.

III.3. STUDY PERIOD AND DURATION

The study period was of 5 years, from 1st January 2018 to 31st December 2022. The study duration was of 9 months with protocol writing, data collection, data analysis and final thesis report from December 2023 to August 2024.

III.4. STUDY POPULATION AND SAMPLING

The study involved a target population of women of reproductive age. Source population involved medical records of patients with ectopic pregnancy who consulted at the YGOPH and YCH from 1st January 2018 to 31st December 2022 and had received inpatient treatment. A consecutive (1 control before and 2controls after the case) and exhaustive sampling method was used. Cases were IUEP and controls were tubal EP with a matching ratio of 1:3, that is one IUEP for three tubal EP with files of patients managed at the same study site.

Inclusion criteria; this study included patients' files with diagnosis of ectopic pregnancy during the study period.

Exclusion criteria; We excluded patients' files with incomplete information, heterotopic and those with a non-surgical management.

Sample size calculation

The minimum sample size was calculated using **Schlesselman's formula** below:

$$\text{Sample size} = \frac{r+1}{r}\frac{(p^*)(1-p^*)(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

Sample size: minimal size for both groups

Ratio of cases to controls, r: 1/3

Average proportion of exposed, P*: (P1+P2)/2

Standard normal variate for level of significance (95%C.I.), Z α/ 2:1.96

Standard normal variate for power (80%), Zβ: 0.84

A previous miscarriage prevalence rate among non-tubal pregnancies (by Aderemi et al., 2015), P1:36.2%

P2 is estimated as the proportion of same exposure in the control group for an OR of 6

After applying the above values in the Schlesselman's formula, N=88. Hence, the groups had at least 22 cases for 66 controls with a minimum total sample size of 88 participants.

III.5. STUDY PROCEDURES

First ethical clearance was obtained from the ethics committee of the Faculty of Medicine and Biomedical Sciences and administrative clearances were obtained from the various hospital authorities after copies of the protocol were deposited and examined by the above institutions. For data collection in the hospitals, we started by exploration of theatre registers where cases of ectopic pregnancy managed surgically were identified, the date of surgery and the locations noted. The next step was to search at the archives the files of all patients with IUEP and those with tubal ectopic pregnancy (in the sequence 1 tubal EP before and 2 after the occurrence of an IUEP). Eligible records for the study were then examined. This procedure was done by the principal investigator with the assistance of the service personnel. We used an interviewer-administered questionnaire designed for the study to collect data. The questionnaire included; socio-demographic data (age, sex, ethnicity, marital status, level of education, occupation) and clinical data collected from patients' medical records (period, risk factors, physical exam, diagnosis, per-operative findings, subsequent pregnancy if any and its outcome). Patients were called over the phone for further data. The questionnaires were checked and validated then data entry into software as early as collected.

III.6. DATA MANAGEMENT AND DATA ANALYSIS

Data collected was entered into CSPro version 7.7 software and the data base exported for analysis in SPSS version 25 software. For descriptive analysis, means and standard deviations were used to describe continuous variables, while frequencies and percentages were used to describe categorical data. Tables and figures were used to represent data. Univariate data analysis was done to assess for factors associated with IUEP compared to Tubal EP with p-values obtained from Chi-square tests (comparing proportions) and Student's t-test (comparing means). Odd's ratios with their 95% Confidence intervals were used to estimate the magnitude and direction of associations. Multivariate analysis was done by logistic regression to control for the effect of confounders. Statistical significance was set at 5%.

III.7. ETHICAL CONSIDERATIONS

This study was carried out after the approval from the Institutional Review Board (IRB) of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I and the Directors of the 2 hospitals. Patients' confidentiality was respected in the handling of their information and results. Data collected was used only for the study purpose.

III.8. TIMELINE

Table III: Gantt chart

Activities	Oct 2023-Jan 2024	Feb-Jul 2024	Aug-Sep 2024
Protocol defence			
Ethical clearance			
Administrative approval			
Purchase of material			
Data collection			
Data processing			
Thesis report writing And Defence			

III.9. RESOURCES NEEDED

Human resources: Those concerned were the main investigator carrying out the study, the supervisors, assisting personnel (medical students, archives personnel etc…).

Material resources: The equipment required for the work were Questionnaires, patients' medical records, laptop and internet.

Table IV: Itemised budget

ITEM	QUANTITY	UNIT PRICE (FCFA)	TOTAL PRICE (FCFA)
Protocol printing	6	2500	15000
Questionnaires printing	300	100	30000
Internet services	6 months	10000/month	60000
Motivation of assistants			40000
Printing Thesis document	6	5000	30000
Transport	6 months		90000
Miscellaneous			50000
Total			**309000**

CHAPTER IV : RESULTS

The study duration was 9 months including protocol writing, data collection, data analysis and final thesis report from December 2023 to August 2022, and we obtained the following results.

In our study we found a total of 1014 ectopic pregnancies amongst which 78 intrauterine. Only 41 cases analysed (due to 34 files not found at archives after search and 03 incomplete) against 123 controls **(Figure12).**

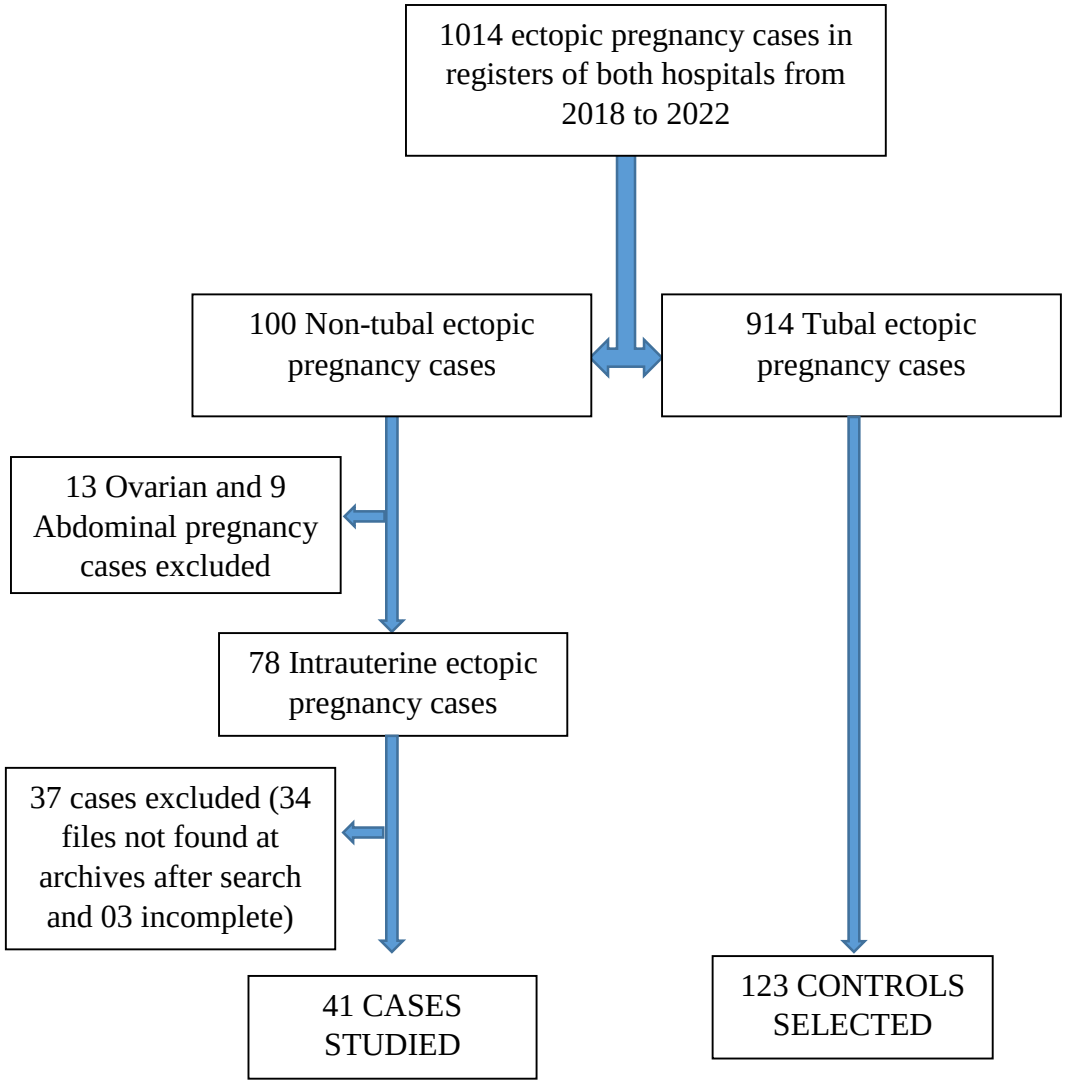

Figure 12 : Participant Recruitment Flow Chart

IV.1. DISTRIBUTION OF ECTOPIC PREGNANCIES WITH LOCATION

IV.1.1. Socio-demographic characteristics of the case-control study population description

The age of participants both groups combined ranged from 18-42 years with a mean of 27.7 (±5.4) years. The most represented age category of the entire study population was 21 – 30 years (65.2%). Majority (66.2%) had secondary education and most of the patients (62.2%) were single.

IV.1.2. Proportion of intrauterine ectopic pregnancy among ectopic pregnancies

We observed a proportion of **7.7%** of intrauterine pregnancies amongst all ectopic pregnancies in our study **(Figure 13).**

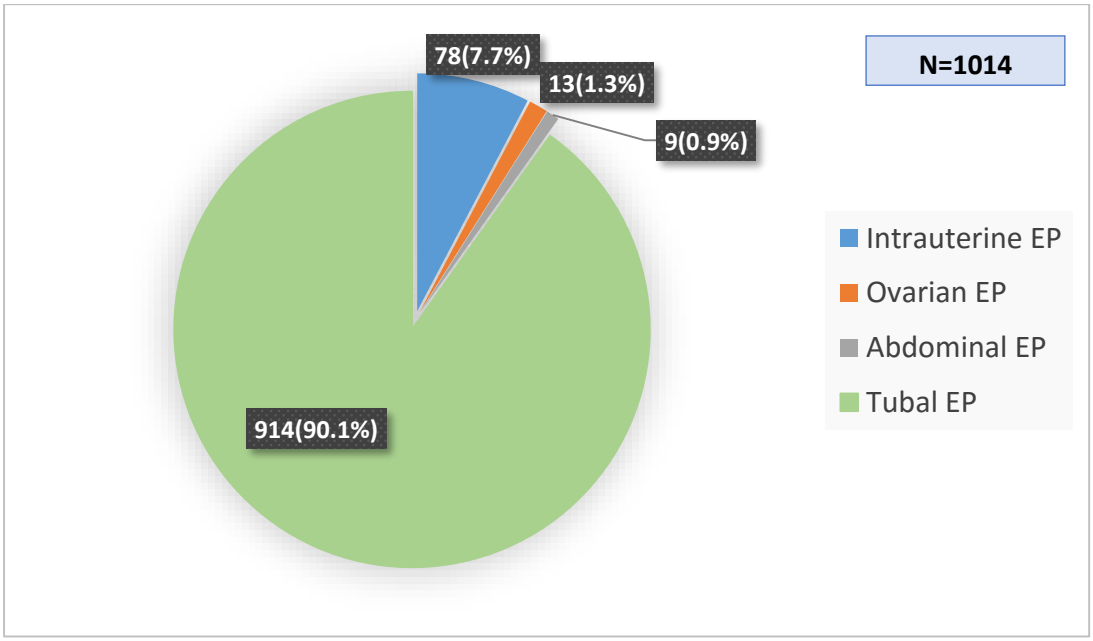

Figure 13 : Proportion of intrauterine ectopic pregnancy among all ectopic pregnancies

IV.1.3. Distribution of all ectopic pregnancies according to location

Non-tubal ectopic pregnancies made up 9.9% of all ectopic pregnancies. Most tubal ectopic pregnancies (80.8%) were ampullary **(Table V).**

Table V: Distribution of all ectopic pregnancies' location

Variable	Frequency (n), N=1014	Percentage (%)
Non-tubal	**100**	**9.9**
Intrauterine	78	78.0
Cornual	53	53.0
Interstitial	25	25.0
Cervical	0	0.0
Cervical scar	0	0.0
Ovarian	13	13.0
Abdominal	9	9.0
Tubal	**914**	**90.1**
Ampullary	739	80.8
Isthmic	133	14.6
Infundibular	42	4.6

IV.1.4. Clinical and paraclinical features of intrauterine ectopic pregnancies

Out of 41 cases of cornual ectopic pregnancy surveyed, 19 (46.3%) did an ultrasound and only 2 **(10.5%) ultrasounds** were in favour of a cornual pregnancy. Also, gestational ages at presentation varied between **6weeks and 20 weeks.** About **85.4%** presented in a state of hemodynamic instability **(Table VI).**

Table VI: Clinical and Paraclinical findings of intrauterine ectopic pregnancy cases

Variable	Frequency (n), N=41	Percentage (%)
Gestational age at presentation		
Min-Max	6 weeks – 20 weeks	
Mean (±sd)	9 weeks 4 days	
Haemodynamic instability	**35**	**85.4**
Presence of Signs of peritoneal irritation	37	90.2
Ultrasound done	19	46.3
Ultrasound report of extra-uterine gestational sac [N=19]	13	68.4
Ultrasound report of cornual location of gestational sac [N=19]	**2**	**10.5**
Peroperative finding of ipsilateral salpingectomy	4	9.8

IV.2. SOCIO-DEMOGRAPHIC CHARACTERISTICS ASSOCIATED WITH IUEP

IV.2.1. Demographic characteristics associated with IUEP

There was a statically significant association between the age group 31 – 40 years and the outcome (**p=0.023**), with this age group being 2.40 times more likely to be found in IUEP compared to tubal EP (OR: 2.40; 95%CI: 1.12-6.47), **Table VII.**

Table VII: Univariate analysis of ectopic pregnancy type and demographic variables

Variable	Cases (IUEP) n (%), N=41	Controls (Tubal EP) n (%), N=123	OR[95%CI]	p-value
Age (years)				
Mean (±sd)	28.9 (±6.1)	27.3 (±5.1)	---	0.107*
Age group				
[15 – 20]	1 (2.4)	10 (8.1)	0.28 [0.09-1.11]	0.094
[21 – 30]	22 (53.7)	85 (69.1)	0.52 [0.19-3.47]	0.501
[31 – 40]	**17 (41.5)**	**28 (22.8)**	**2.40 [1.12-6.47]**	**0.023**
[41 – 50]	1 (2.4)	0 (0.0)	---	0.087

**p-value from student's t test, EP=Ectopic Pregnancy, sd=standard deviation, IUEP=intrauterine ectopic pregnancy*

IV.2.2. Socio-cultural characteristics associated with IUEP

There was no significant association between level of education nor employment status IUEP **(Table VIII).**

Table VIII: Univariate analysis of ectopic pregnancy type and socio-cultural variables

Variable	Cases (IUEP) n (%), N=41	Controls (Tubal EP) n (%), N=123	OR[95%CI]	p-value
Level of education				
Primary	1 (3.3)	6 (5.7)	0.49 [0.27-1.51]	0.254
Secondary	18 (60.0)	72 (67.9)	0.55 [0.28-1.94]	0.516
Higher	11 (36.7)	28 (26.4)	1.24 [0.84-5.37]	0.431
Occupation				
Civil servant	1 (2.5)	6 (4.9)	0.49 [0.21-1.76]	0.243
Private sector	17 (42.5)	42 (34.1)	1.37 [0.72-6.88]	0.299
Housewife	10 (25.0)	28 (22.8)	1.09 [0.81-4.56]	0.476
Unemployed	4 (10.0)	4 (3.3)	3.22 [0.95-8.98]	0.062
Student	8 (20.0)	43 (35.0)	0.45 [0.14-1.18]	0.089
Marital status				
Single	22 (53.7)	80 (65.0)	0.62 [0.36-1.28]	0.256
Married	13 (31.7)	29 (23.6)	1.51 [0.79-4.42]	0.427
Cohabiting	6 (14.6)	14 (11.4)	1.34 [0.82-3.51	0.580
Religion				
Christian	34 (82.9)	107 (87.0)	0.20 [0.06-1.73]	0.810
Muslim	6 (14.7)	13 (10.6)	1.45 [0.76-4.25]	0.541
Others	1 (2.4)	3 (2.4)	1.00 [0.87-5.48]	0.987
Region of Origin				
South	2 (4.9)	5 (4.1)	1.21 [0.86-6.03]	0.725
Far North	0 (0.0)	3 (2.4)	---	0.084
North	1 (2.4)	6 (4.9)	0.49 [0.21-1.94]	0.590
Centre	14 (34.2)	39 (31.7)	1.12 [0.75-3.89]	0.783
West	20 (48.8)	47 (38.2)	1.54 [0.81-3.30]	0.349
North-west	1 (2.4)	5 (4.1)	0.59 [0.20-1.37]	0.242
South-west	2 (4.9)	9 (7.3)	0.65 [0.39-2.34]	0.403
Littoral	1 (2.4)	8 (6.5)	0.36 [0.16-1.88]	0.330
East	0 (0.0)	1 (0.8)	---	0.075

EP=Ectopic Pregnancy, IUEP=intrauterine ectopic pregnancy

IV.3. CLINICAL CHARACTERISTICS ASOOCIATED WITH IUEP

IV.3.1. Association with obstetric history

Neither gravidity nor parity had a significant association with IUEP compared to tubal pregnancy **(Table IX).**

Table IX: Univariate analysis of ectopic pregnancy type and obstetrics history variables

Variable	Cases (IUEP) n (%), N=41	Controls (Tubal EP) n (%), N=123	Total n (%), N=164	OR[95%CI]	p-value
Gravidity					
Primigravid (1)	7 (17.1)	22 (17.9)	29 (17.7)	0.95 [0.37-2.41]	0.906
Multigravida (≥2)	34 (82.9)	101 (82.1)	135 (82.3)	1.05 [0.42-2.70]	
Parity					
Nullipara (0)	8 (19.5)	41 (33.4)	49 (29.9)	0.49 [0.27-1.81]	0.331
Primipara (1)	14 (34.2)	26 (21.1)	40 (24.4)	1.94 [0.83-5.21]	0.258
Multipara (2-4)	16 (39.0)	48 (39.0)	64 (39.0)	1.00 [0.85-3.40]	0.984
Grand multipara (≥5)	3 (7.3)	8 (6.5)	11 (6.7)	1.14 [0.89-2.11]	0.763

EP=ectopic pregnancy, UIEP=intrauterine ectopic pregnancy

IV.3.2. Association with risk factors for ectopic pregnancy

Three factors had a statistically significant association between IUEP compared to tubal pregnancy. Two being more likely in IUEP; Ipsilateral salpingectomy **p=0.004, (OR: 13.19; 95%CI: 1.43-121.68)** and Previous ectopic pregnancy **p=0.024, (OR: 3.41; 95%CI: 1.12-10.42)** while PID was more likely in tubal **p=0.019, OR:0.42; 95%CI: 0.20-0.88, (Table X).**

Table X: Univariate analysis of ectopic pregnancy type and risk factors for ectopic pregnancy

Variable	Cases (IUEP) n (%), N=41	Controls (Tubal EP) n (%), N=123	Total n (%), N=164	OR[95%CI]	p-value
History of Abortion	14 (34.1)	57 (46.3)	71 (43.3)	0.60 [0.29-1.25]	0.172
History of Ectopic pregnancy	7 (17.1)	7 (5.7)	14 (8.5)	**3.41 [1.12-10.42]**	**0.024**
History of modern Contraception use	5 (12.2)	21 (17.6)	26 (16.3)	0.65 [0.23-1.85]	0.414
Documented tubal pathology	2 (4.9)	0 (0.0)	2 (1.2)	---	0.014
History of Infertility	0 (0.0)	1 (0.8)	1 (0.6)	---	0.563
ART	0 (0.0)	0 (0.0)	0 (0.0)	---	---
Passed history of PID	15 (36.6)	71 (57.7)	86 (52.4)	**0.42 [0.20-0.88]**	**0.019**
Cumulative life sexual partners number					
Mean (±sd)	2.54 (±1.55)	3.41 (±1.73)	3.1 (±1.73)	---	0.005*
Smoking	1 (2.4)	5 (4.1)	6 (3.7)	0.59 [0.07-5.20]	0.631
Previous pelvic surgery	7 (17.1)	18 (14.6)	25 (15.2)	1.20 [0.46-3.12]	0.707
Appendectomy	0 (0.0)	3 (2.4)	3 (1.8)	---	0.313
Peroperative finding of ipsilateral salpingectomy	4 (9.8)	1 (0.8)	5 (3.0)	**13.19 [1.43-121.68]**	**0.004**

**p-value from student's t test, artificial reproductive technics (ART), pelvic inflammatory disease (PID)*

IV.3.3. Independent associations

Following univariate analysis, statistically significant variables were included into a logistic regression model for multivariate analysis. Three factors (age group of 31-40 years, ipsilateral salpingectomy and PID) were found to be independently associated with the outcome of IUEP compared to tubal EP **(Table XI).**

Table XI: Multivariate Analysis for factors independently associated with cornual ectopic pregnancy compared to tubal ectopic pregnancy

Variable	OR [95%CI]	p-value	aOR[95%CI]	ap-value
31 – 40 years age group	2.40 [1.12-6.47]	0.023	**2.42 [1.23-4.74]**	**0.010**
History of Ectopic pregnancy	3.41 [1.12-10.42]	0.024	2.83 [0.79-10.20]	0.110
PID	0.42 [0.20-0.88]	0.019	**0.38 [0.17-0.82]**	**0.014**
Peroperative finding of ipsilateral salpingectomy	13.19 [1.43-121.68]	0.004	**6.41 [1.07-60.51]**	**0.042**

aOR=adjusted odds ratio, ap-value=adjusted p-value

IV.4. SUBSEQUENT PREGNANCY FOLLOWING IUEP AND OUTCOME

IV.4.1. Conception post-IUEP surgery

Out of the 20 participants that had a desire to conceive 17 (85%) did and conception occurred within 18 months post-surgery in 75% of cases **(Table XII).**

Table XII: conception post-IUEP surgery

Variable	**Frequency (n), N=20**	**Percentage (%)**
Desire for conception		
Yes	20	
No	12	
Conception following IUEP	17	85
Number of months following management		
Min-max	**6 months – 36 months**	
Mean (±sd)	13.35 (±8.98) months	
≤ 18 months	15	75
> 18 months	2	10
Location of pregnancy [N=17]		
Intrauterine	17	100

IV.4.2. Outcome of pregnancy post-IUEP surgery

Ten pregnancies reached 3rd trimester with 7 (41.1%) term deliveries, vaginal (3) and caesarean section (4). No uterine rupture occurred **(Table XIII).**

Table XIII: Outcome of pregnancy following management of IUEP ectopic pregnancy

Variable	Frequency (n), N=17	Percentage (%)
Outcome of pregnancy [N=17]		
Term delivery	7	41.1
Preterm delivery	0	0.0
Abortion	7	41.1
Currently pregnant (3rd)	3	11.8
Uterine Rupture	**0**	**0.0**
Route of delivery [N=7]		
Vaginal delivery	3	42.9
Caesarean section	4	57.1
Foetal outcome		
Life	7	100

3rd = 3rd trimester

CHAPTER V : DISCUSSION

In our study, we aspired to identify factors associated with intrauterine ectopic pregnancy and the outcome of subsequent pregnancies in two hospitals in Yaounde. We used a case-control study design to evaluate various locations of ectopic pregnancy, their socio-demographic and clinical aspects and outcome of subsequent pregnancies at YCH and YGOPH. These 2 hospitals being the most used for obstetrics and gynaecological purpose in the city. In our study we found a total of 1014 ectopic pregnancies amongst which 78 intrauterine. Only 41 cases analysed for associations (due to 34 files not found at archives after search and 03 incomplete) against 123 controls.

V.1. DISTRIBUTION OF ECTOPIC PREGNANCIES WITH LOCATION

V.1.1. Socio-demographic characteristics of the study population

The age of participants ranged from 18-42 years with a mean of 27.7 (±5.4) years. This is similar to the results of 27.68±5.5 years by Atabong *et al*[23] and 28.5±5.9 years by Fouedjio *et al*[50]. The most (65.2%) represented age category of the study being 21 – 30 years as in both studies above[23,50]. The fact that this age range is the most reproductive age group (with more pregnancies) could explain why they are more likely to be found with ectopic pregnancies. Over half of our participants (62.2%) were single, having no formal employment (59.5%) and about three quarter (71.3%) not having a university education. This suggests that women with poor socioeconomic status could be more likely to be affected by ectopic pregnancy.

V.1.2. Proportion of intrauterine ectopic pregnancy among ectopic pregnancies

Out of the1014 ectopic pregnancies registered, we had 9.9% non-tubal and 90.1% tubal, close to the 5-8.3% proportion of non-tubal EP among all EPs reported in Italy by Stabile *et al*[51] but lower than 20% reported by Naik *et al* [52] in a tertiary hospital in India. They justified their high value with the reason that their health facility was the reference centre in the area. We couldn't find any other reason for the difference in results.

Among all EPs, 0.9% were abdominal, 1.3% ovarian, and 7.7% IUEP (cornual/interstitial). We had similar proportion of abdominal and ovarian pregnancy to Tang et al[53]. However, the 7.7 for cornual-interstitial pregnancy is higher than the 2-5% reported in some literature reviews[9,14,31]. This could be explained by the fact that only cases manage surgically were considered in our study, given that these cases usually present late necessitating surgery.

V.1.3. Other ectopic pregnancy localisations

Among the tubal pregnancies, the ampulla remains the most frequent site (80%) followed by isthmic (14.6%) and infundibular (4.6%) pregnancies, similar distribution were reported by Fouedjio *et al*[50] and Shan *et al*[13].

V.1.4. Clinical and Paraclinical findings of intrauterine ectopic pregnancies

Patients presented at a gestational age ranging from 6 to 20weeks, findings similar to those of Alalade et al[2] and time of rupture at 7–16 weeks of gestation reported by Yang et Liu[9] in their review.[2,9] These pregnancies rupture at later gestational ages because the proximal portion of the fallopian tube (interstitial) is surrounded by the muscular wall of the uterus, the greater distensibility of the myometrium covering this portion allowed pregnancy to proceed to a more advanced stage before it ruptures, which can be as late as the 7^{th} to 16^{th} week of gestation[9] and in extremely rare cases reach 3^{rd} trimester with a viable foetus as in a case reported by Rathod et al[5].

Out of all the cases of IUEP, 85.4% presented with haemodynamic instability. This goes in line with reports of literature as presented by Yang et Liu[9], this has been explained by the fact this site is highly vascularised and ectopic pregnancy rupture here can lead to catastrophic haemorrhage within a short period of time. Another important reason behind this could be linked to the delay of arrival in the hospital of patients with EP due to lack of knowledge as reported by Liu *et al*[54] and also known difficulties in diagnosis of these cases of IUEP[37].

Out of the 19 cases that had an ultrasound result only 10.5% had finding in favour of an IUEP (cornual), this result is consistent with the difficulty in identifying the exact location of ectopic pregnancy as reported by Chen et al[33]. However, it is lower than the 65% reported by Ng *et al*[49] and 100% of correct diagnosis for cornual pregnancies reported by Alalade *et al*[2] in their study. This difference in results could be explained by the fact that most ultrasound results recorded in our study were from other radiologic centres than those of our study site with qualification of ultrasound operator not known. This suggests that exact localisation of these pregnancies could depend on the expertise of the ultrasound operator and the quality of ultrasound machine used.

V.2. SOCIO-DEMOGRAPHIC CHARACTERISTICS ASSOCIATED WITH IUEP COMPARED TO TUBAL ECTOPIC PREGNANCIES

AGE

There was a statically significant association between the age group ≥31 years and IUEP, p=0.023 with IUEP being more likely to be observed in this age group compared to tubal EP (OR: 2.40; 95%CI: 1.12-6.47) this goes in line with the findings of Alalade *et al*[2] in whose study 57.8% of participants with cornual pregnancy being of this age group. A possible explanation could be that at this age, patients have probably been exposed to other factors for example PID with its chronic manifestations in the pelvis. Also, tubal function changes related to age and increase in chromosomal abnormalities in trophoblastic tissue have been reported to favour EP[20].

In our study, the level of education, marital status, and employment status had no statistically significant association with IUEP, we didn't find any contrary finding in literature

V.3. CLINICAL CHARACTERISTICS ASSOCIATED WITH IUEP COMPARED TO TUBAL ECTOPIC PREGNANCIES

V.3.1. Association with obstetric history

❖ **Gravidity and Parity**

Primigravid and multigravida in both cases and controls had similar proportions in our study. Alalade et al[2] described 37% of patients with IUEP that were primigravid, this was descriptive, hence no significant proof. We had 34.2% of primipara with IUEP compared to 21.1% with tubal pregnancy though it was not statistically significant. The other groups of gravidity had similar proportions in both IUEP and tubal EP compared. Just like us, Alalade et al[2] had no statistically significant association between parity and IUEP. Shan et al[13] on the other hand describe more multipara (≥2) that is, 61.9% with IUEP than tubal EP that is, 51.5% but did not show any significant difference. We couldn't find other articles comparing gravidity and parity.

V.3.2. Association with risk factors for ectopic pregnancy

❖ **Passed history of ectopic pregnancy**

We found a statistically significant association between passed history of ectopic pregnancy and IUEP (p=0.024), with a history of EP being 3.41 times more likely to be found in IUEP than in tubal ectopic pregnancy (OR: 3.41; 95%CI: 1.12-10.42). This result is consistent with the report of Chen *et al*[14] in their review who mentioned that, previous EP was one of the most common risk factors for IP (40.6%). Contrary to what we found, both Shan *et al* and Alalade

et al found no statistically significant association between previous ectopic pregnancy and non-tubal EP[2], This difference in results could mean that other factors are possibly implicated thus requiring further investigation.

❖ **Passed history of PID**

There was a significant association between PID and IUEP (p=0.019), but it was less likely to occur in IUEP than tubal EP in this category (OR: 0.42; 95%CI: 0.20-0.88). Contrary to findings of; Alalade *et al*[2] who had a significant association between PID and cornual pregnancy as all patients in the non-tubal EP group with PID had a diagnosis of cornual EP, Shan *et al*[13] found that PID was significantly higher in cornual EP than in tubal EP (p<0.01) and Chen *et al*[14] whose literature review noted PID as one of the most common factors of IP, given that some articles report that damaged tubed are found more often in proximal ectopic pregnancies than in distal[34,55]. This difference in results could be due to the fact that we considered a case to have PID only when it was written in the file mean while due to the retrospective nature of the study, we are uncertain that this factor was explored for every patient.

❖ **Ipsilateral salpingectomy**

As reported in several literature reviews as the single most important risk factor for cornual/interstitial EP[12,14,34], ipsilateral salpingectomy was found to be significantly associated with IUEP pregnancy (p=0.004), 13.19 times more likely to be found in patients with IUEP than tubal (OR: 13.19; 95%CI: 1.43-121.68). It is believed that after a total salpingectomy, there is an aseptic inflammation at the uterine horn which produces chemokines, that may favour embryonic migration to and implantation at this site. Hence it may explain why previous salpingectomy could increase the rate of IP[14].

❖ **History of abortion**

History of abortion in our study was not associated to IUEP similar to the findings of Shan *et al*[13], no other reviewed identified this as an associated factor. Unlike our results, those of Alalade *et al*[2] had previous miscarriage as an associated factor non-tubal ectopic pregnancy in this same study. We think that those with miscarriage in the other study probably had other factors like PID for example which in the same study was also an associated factor.

There was no statistically significant association between IUEP and smoking, pelvic surgery, previous tubal surgery and contraception. We had no case of assisted reproduction in our study so association couldn't be evaluated.

V.3.3. Independent associations

Following multivariate analysis with logistic regression model 3 factors were found to be independently associated with IUEP. Two of them being more likely to be found in IUEP than in tubal EP; age ≥31 years (ap=0.010), aOR: 2.42; 95%CI: 1.23-4.74 and ipsilateral salpingectomy (ap= 0.042), aOR: 6.41; 95%CI: 1.07-60.51. On the other PID was less likely (ap=0.014), aOR: 0.38; 95%CI: 0.17-0.82. Ipsilateral salpingectomy had an expected result as discussed in literature by Chen *et al*, Gaetani et al and Houda *et al*[12,14,34], none of which had mentioned age as an associated factor. This could be because there are tubal function changes related to age and increase in chromosomal abnormalities in trophoblastic tissue[20], also more and more women deliver at older ages together with. On the other hand, PID here is found to be less likely in IUEP, the difference could be due to the fact that this variable was not properly explored.

V.4. OUTCOME OF SUBSEQUENT PREGNANCY

V.4.1. conception post- surgery for IUEP

Out of the 41 cases, 17 conceived and all being intrauterine, 3 had a desire but had not conceived yet, 12 had no desire for conception (under contraception or abstinence). Nine of them could not be contacted. We observed a better fertility outcome (85%) in those who had a desire to conceive than Boychuk *et al*[56] in Ukraine who reported a 60% infertility post-salpingectomy and Poordast *et al*[57] in Iran who had 53.6% of pregnancy occurrence post salpingostomy. Our findings were similar to those of Liao *et al*[58] in Taiwan who had 71.4% of conception in those that had a desire. On the other hand, Svenningsen *et al*[59] in Oslo found no difference in fertility rate between tubal and interstitial pregnancy post-cornual resection. The higher outcome in our result could be linked to the small sample we had and also the fact that we couldn't contact some (selection bias). Conception after 18 months post-surgery occurred in 75% of cases. This is just slightly lower than the 85% chances of conception after 12 months of conception as described by Taylor[60]. We considered 18 months in our study because we estimated a 6 months period for post-op recovery. This is an expected result given that the patients now present fertility lowering factors. In a randomised control trial conducted in France by Fernandez *et al*[61] only 64% of patients conceived till 2 years after radical surgery for tubal EP. The difference in our results could be related to selection bias in our study.

The time between surgery and conception being 6-36 months with a mean of 13.35 (±8.98) months, a similar result of 2–53 months interval with a mean of 16 months was obtained in Singapore by Ng *et al*[49].

V.4.2. outcome of pregnancy post-surgery for IUEP

Seven had an abortion and 10 pregnancies evolved till at least 30 weeks. Three were still pregnant at the moment data collection ended and the other 7 had delivered at term. This is consistent with report in literature that though there is fear of uterine rupture these pregnancies can reach term. The routes of delivery were vaginal (3) and caesarean section (4), Svenningsen *et al*[59] in their study in Oslo had more (60%) cases that delivered by caesarean section. Ng *et al*[49] had 50% vaginal deliveries, 30% caesarean sections and 20% lost to follow-up. Lee *et al*[47] in Seoul reported a case of term pregnancy after laparoscopic cornual resection on same pregnancy for heterotopic cornual pregnancy, and delivered by emergency caesarean section for failure of labour to progress. Tompeen *et al*[62] had a case of twin pregnancy 7 months post-laparoscopic cornual resection who delivered by caesarean section at 37 weeks. Although vaginal delivery is possible, caesarean section is still thought to be the safest route due to fear of uterine rupture during labour, the sample size is still too small to confirm safety of vaginal deliveries.

Just like Ng *et al* and Nikodijevic *et al*[10,49] we recorded no uterine rupture in our study, on the other hand, Svenningsen *et al*[59] recorded 2 cases of uterine rupture out of 33 pregnancies and Liao *et al*[58] 30% incidence of uterine rupture. The difference in our results could be due to the small number of term pregnancies in our study and information not gotten from all patients. Another reason could be proper counselling post-surgery and follow-up by qualified personnel.

V.5. LIMITATIONS

This study had the following limitations:

1. This study involved participants in 2 hospitals only, as a result some factors and subtypes of EP were not represented.
2. Only files of patients managed surgically were involved hence missing other cases. However, only these cases could have definitive diagnosis of location.
3. Many files were unexplored due to their absence or missing information, given that it was a retrospective study.
4. Some information could not be obtained due to recall bias.

CONCLUSION

From our results we can conclude that;

1. IUEP is a fairly common localisation of ectopic pregnancy. The diagnosis before surgery is difficult and management is late.
2. The only identified socio-demographic factor associated with IUEP was age ≥31 years which was independently associated.
3. Identified clinical factors associated with IUEP include; history of ipsilateral salpingectomy with increasing odds and independently. PID on the other hand was independently less likely to be found in IUEP than in tubal EP. Previous ectopic pregnancy was also associated with increasing odds but was not independently associated.
4. Subsequent pregnancies can reach term with a favourable outcome and most deliveries were by caesarean section.

RECOMMENDATIONS

Looking at our findings, we make the following recommendations to;

Ministry of Public Health

1. Should develop policies targeting late management hence reducing morbidity.

Health institutions and clinicians

1. The presence of associated factors identified above should raise suspicion for early diagnosis of IUEP and appropriate anticipation of management technics and material made.
2. Radiologists should have in mind that IUEP is fairly common and should search for ultrasound signs especially in patients with associated factors observed.

Women of reproductive age

1. Women of reproductive age should consult immediately amenorrhoea is noticed or any suspicion of pregnancy, especially those; aged ≥ 31 years, with history of ectopic pregnancy and salpingectomy.
2. Women with IUEP should know the high likelihood of caesarean section if they desire to conceive again.

Researchers

1. Further research on the topic with a larger sample size, a cohort design is necessary, especially on aspects like PID and ectopic pregnancy as associated factors and outcome of subsequent pregnancies.

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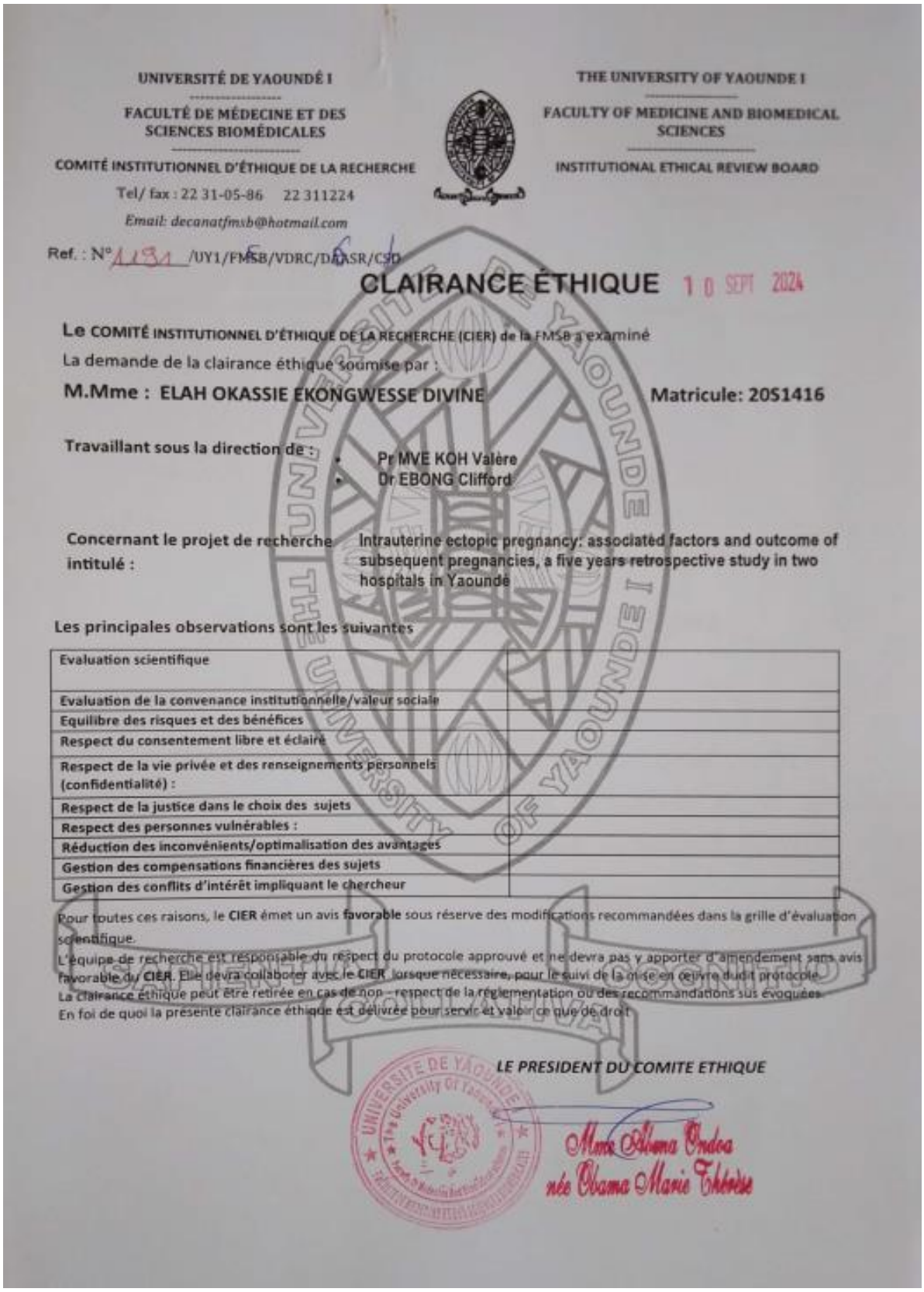
APPENDICES

APPENDIX I: FACULTY ETHICAL CLEARANCE



UNIVERSITÉ DE YAOUNDÉ I

FACULTÉ DE MÉDECINE ET DES SCIENCES BIOMÉDICALES

COMITÉ INSTITUTIONNEL D'ÉTHIQUE DE LA RECHERCHE

Tel/ fax : 22 31-05-86 22 311224

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THE UNIVERSITY OF YAOUNDE I

FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES

INSTITUTIONAL ETHICAL REVIEW BOARD

Ref. : N°1191/UY1/FMSB/VDRC/DAASR/CSD

CLAIRANCE ÉTHIQUE 10 SEPT 2024

Le COMITÉ INSTITUTIONNEL D'ÉTHIQUE DE LA RECHERCHE (CIER) de la FMSB a examiné

La demande de la clairance éthique soumise par :

M.Mme : ELAH OKASSIE EKONGWESSE DIVINE **Matricule: 20S1416**

Travaillant sous la direction de :

- Pr MVE KOH Valère
- Dr EBONG Clifford

Concernant le projet de recherche intitulé : Intrauterine ectopic pregnancy: associated factors and outcome of subsequent pregnancies, a five years retrospective study in two hospitals in Yaoundé

Les principales observations sont les suivantes

Evaluation scientifique	
Evaluation de la convenance institutionnelle/valeur sociale	
Equilibre des risques et des bénéfices	
Respect du consentement libre et éclairé	
Respect de la vie privée et des renseignements personnels (confidentialité) :	
Respect de la justice dans le choix des sujets	
Respect des personnes vulnérables :	
Réduction des inconvénients/optimalisation des avantages	
Gestion des compensations financières des sujets	
Gestion des conflits d'intérêt impliquant le chercheur	

Pour toutes ces raisons, le **CIER** émet un avis **favorable** sous réserve des modifications recommandées dans la grille d'évaluation scientifique.

L'équipe de recherche est responsable du respect du protocole approuvé et ne devra pas y apporter d'amendement sans avis favorable du **CIER**. Elle devra collaborer avec le **CIER** lorsque nécessaire, pour le suivi de la mise en œuvre dudit protocole.

La clairance éthique peut être retirée en cas de non - respect de la réglementation ou des recommandations sus évoquées.

En foi de quoi la présente clairance éthique est délivrée pour servir et valoir ce que de droit

LE PRESIDENT DU COMITE ETHIQUE

Mme Obama Ondoa née Obama Marie Thérèse

APPENDIX II: YGOPH ETHICAL CLEARANCE

REPUBLIQUE DU CAMEROUN
Paix-Travail-Patrie
MINISTERE DE LA SANTE PUBLIQUE
HOPITAL GYNECO-OBSTETRIQUE ET PEDIATRIQUE DE YAOUNDE
HUMILITE – INTEGRITE – VERITE - SERVICE

REPUBLIC OF CAMEROON
Peace-Work-Fatherland
MINISTRY OF PUBLIC HEALTH
YAOUNDE GYNAECO-OBSTETRIC AND PEDIATRIC HOSPITAL
HUMILITY – INTEGRITY – TRUTH - SERVICE

COMITE INSTITUTIONNEL D'ETHIQUE DE LA RECHERCHE POUR LA SANTE HUMAINE (CIERSH)

Arrêté n° 0977 du MINSANTE du 18 avril 2012 portant création et organisation des Comités d'Ethiques de la Recherche pour la santé Humaines. (CERSH).

AUTORISATION N° 776 /CIERSH/DM/ATTD/2024

CLAIRANCE ETHIQUE

Le Comité Institutionnel d'Ethique de la Recherche pour la Santé Humaine (CIERSH) a réexaminé le 6 Aout 2024, la demande d'autorisation et le Protocole de recherche intitulé **« intrauterine ectopic pregnancy : associated factors and outcome of subsequent pregnancies, a five years retrospective study in two hospitals in Yaounde»** soumis par le Docteur ELAH OKASSIE EKONGWESSE DIVINE.

Le sujet est digne d'intérêt. Les objectifs sont bien définis. La procédure de recherche proposée ne comporte aucune méthode invasive préjudiciable aux participants. Le formulaire de consentement éclairé est présent et la confidentialité des données est préservée. Pour les raisons qui précèdent, le CIERSH de HGOPY donne son accord pour la mise en œuvre de la présente recherche.

le Docteur ELAH OKASSIE EKONGWESSE DIVINE, devra se conformer au règlement en vigueur à HGOPY et déposer obligatoirement une copie de ses travaux à la Direction Médicale de ladite formation sanitaire./-

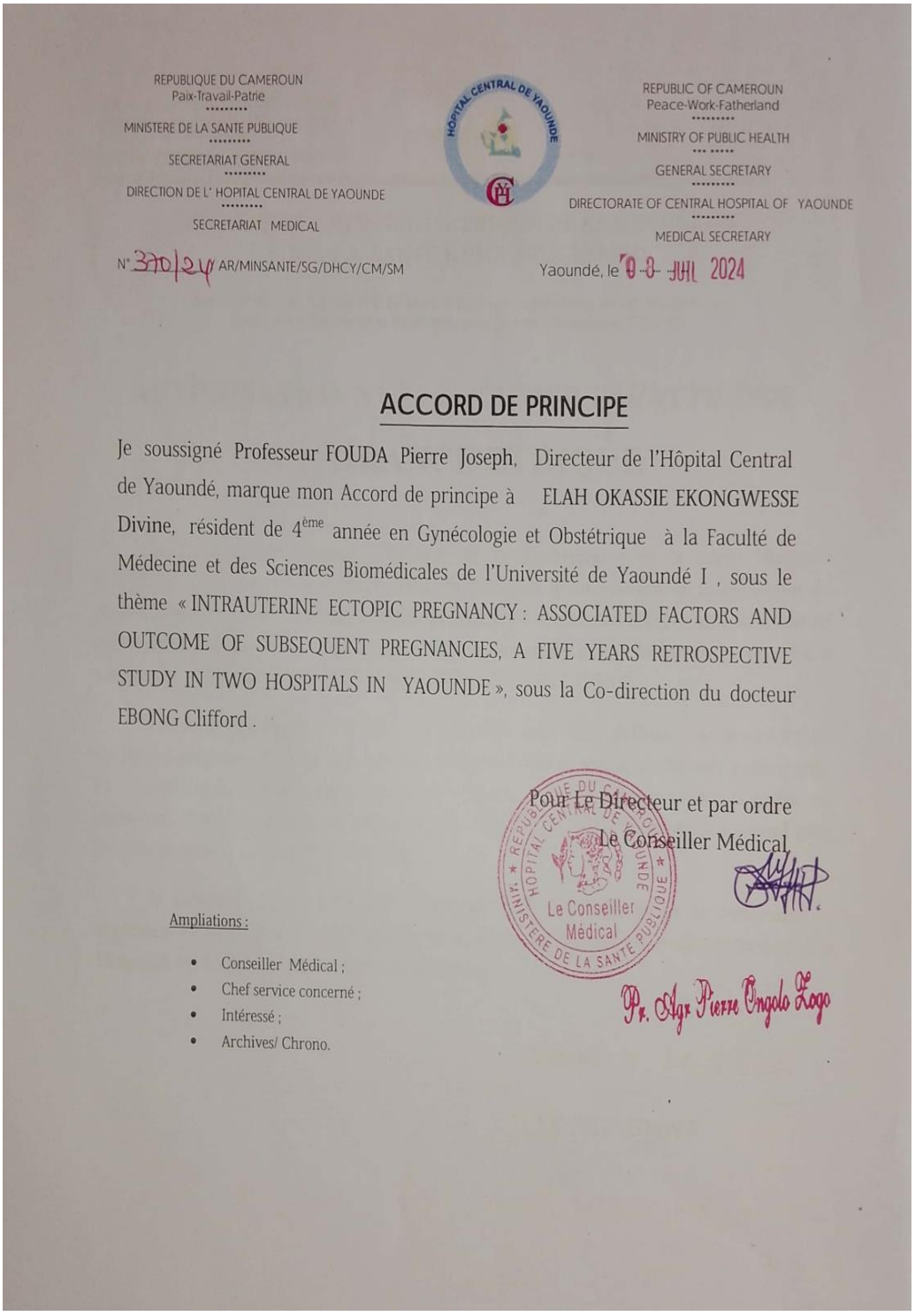
Yaoundé, le 12 AOUT 2024

LE PRESIDENT

Prof MBU Robinson
Directeur Général
HGOPY

N°1827 ; Rue 1564 ; Ngousso ; Yaoundé 5ème
BP : 4362 Tél. : 242 05 92 94 / 222 21 24 33 / 222 21 24 31 Fax : 222 21 24 30
E-mail : hgopy@hotmail.com / hgopy@hgopy.cm

APPENDIX III: YCH ADMINISTRATIVE AUTHORIZATION



REPUBLIQUE DU CAMEROUN
Paix-Travail-Patrie
MINISTERE DE LA SANTE PUBLIQUE
SECRETARIAT GENERAL
DIRECTION DE L' HOPITAL CENTRAL DE YAOUNDE
SECRETARIAT MEDICAL

N° 370/24/ AR/MINSANTE/SG/DHCY/CM/SM

REPUBLIC OF CAMEROUN
Peace-Work-Fatherland
MINISTRY OF PUBLIC HEALTH
GENERAL SECRETARY
DIRECTORATE OF CENTRAL HOSPITAL OF YAOUNDE
MEDICAL SECRETARY

Yaoundé, le 03 JUIL 2024

ACCORD DE PRINCIPE

Je soussigné Professeur FOUDA Pierre Joseph, Directeur de l'Hôpital Central de Yaoundé, marque mon Accord de principe à ELAH OKASSIE EKONGWESSE Divine, résident de 4ème année en Gynécologie et Obstétrique à la Faculté de Médecine et des Sciences Biomédicales de l'Université de Yaoundé I , sous le thème « INTRAUTERINE ECTOPIC PREGNANCY : ASSOCIATED FACTORS AND OUTCOME OF SUBSEQUENT PREGNANCIES, A FIVE YEARS RETROSPECTIVE STUDY IN TWO HOSPITALS IN YAOUNDE », sous la Co-direction du docteur EBONG Clifford .

Pour Le Directeur et par ordre
Le Conseiller Médical

Le Conseiller Médical

Pr. Agr Pierre Engolo Zogo

Ampliations :

- Conseiller Médical ;
- Chef service concerné ;
- Intéressé ;
- Archives/ Chrono.

APPENDIX IV: QUESTIONNAIRE

Title: Intrauterine Ectopic Pregnancy: Associated Factors and Outcome of Subsequent Pregnancies, a Five Years Retrospective Study in Two Hospitals in Yaounde

CODE: _____ HOSPITAL: YGOPH: □ YCH: □ Date:

1. IDENTIFICATION/ SOCIO DEMOGRAPHIC FACTORS		
1.1	**Age:**	_____ years
1.2	**Level of education:**	Primary: □ Secondary: □ University: □ None: □
1.3	**Occupation:**	Civil servant: □ Housewife: □ Self-employed: □ Unemployed: □ Student: □
1.4	**Marital Status**	Single: □ Married: □ Widow: □ Divorced: □ Cohabiting: □
1.5	**Area of residence**	Urban: □ Rural: □
1.6	**Tribe**	
2. PAST HISTORY		
2.1	**Obstetric History**	G P Abortions: 0: □ 1: □ 2: □ 3: □ 4: □ ≥5: □ Previous ectopic pregnancies: 0: □ 1: □ 2: □ ≥3: □
2.2	**Amenorrhea before diagnosis (Weeks/days from LMP)**	Yes: □ (____ weeks + _____ days) No: □ Not sure: □ Spotting seen as menses: □
2.3	**Were you on contraception**	No: □ Yes: □ **If yes, which?** Male Condom: □ Female condom: □ OCP: □ Injection: □ LVG implant: □ IUCD: □ Emergency contraceptive pills in last cycle: □
2.4	**Was pregnancy desired**	Yes: □ No: □ Not sure: □
2.5	**History of abnormal uterine bleeding**	Yes: □ No: □ Not sure: □
2.6	**Gynaecological history**	

Previous ectopic Pregnancy: □ if yes geste done	Previous abortion: □	ART: if yes IVF□ Ovulation induction: □
Previous tubal surgery: □	Infertility: □	Documented tubal pathology
Previous STI: □	Previous PID: □	Life sexual partners number: □
Contraception failure: □	Smoking: □	
Previous pelvic surgery: □	Appendectomy: □	
Others**:**	_____	
3. HISTORY OF ILLNESS and DIAGNOSIS		

3.1	What was the first symptom you had	_____
3.2	**Other symptoms**	Spotting/Bleeding: □ Pelvic pains: □ Fatigue: □ Fainting: □ Amenorrhea: □ Others: _____

3.3	**Physical exam findings on admission**	**General:** Palor: □ Shock: □ Tachycardia >100: □ Hypotention: □ **Abdominal:** Distension: □ Tenderness: □ Rebound tenderness: □ Guarding: □ Normal: □ Other: _____ **Speculum:** Chadwick sign: □ Bleeding: □ None: □ Other: _____ **Digital vaginal exam:** Cervical motion tenderness: □ Forniceal tenderness: □ Adnexal mass: □ Adnexal tenderness: □ None: □ Other: _____
3.4	**Ultrasound Diagnosis**	Was ultrasound done: Yes □ No: □ **If yes, what were the findings?** Intra uterine Pseudosac: Yes □ No: □ Extrauterine sac: Yes □ No: □ If sac seen, was there cardiac activity? : Yes □ No: □ Hemoperitoneum: Yes □ No: □ Volume: _____mL (Small □ Moderate: □ Large □) Intrauterine pregnancy: Yes □ No: □

		localisation: _____
4. PATIENT MANAGEMENT		
4.1	**Surgical management**	Laparotomy: □ Laparoscopy: □
4.2	**Per operative findings**	Hemoperitoneum: Localisation of pregnancy: State of adnexae: Pelvic adhesions:
4.3	**Surgical gest done**	

5. HISTORY OF fertility post-ectopic pregnancy		
5.1	Conception after IUEP Yes □ No □	_____ if yes number of months
5.2	Location	
5.3	Outcome	Abortion Uterine Rupture Terme at delivery Route of delivery___ Still pregnant _____