

**A REVIEW ON PREGNANCY OF UNKNOWN
LOCATION CASES IN HOSPITAL RAJA
PEREMPUAN ZAINAB II (HRPZ II), KOTA BHARU
FROM 2015 UNTIL 2019**

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LIST OF ABBREVIATIONS

AEPU	Association of Early Pregnancy Units
CI	Confidence Interval
EP	Ectopic Pregnancy
EPAU	Early Pregnancy Assessment Unit
FPUL	Failed Pregnancy of Unknown Location
hCG	Human Chorionic Gonadotropin
HRPZ II	Hospital Raja Perempuan Zainab 2
IU/L	International Units per Litre
IUP	Intra Uterine Pregnancy
LNMP	Last Normal Menstrual Period
METEX	Methotrexate versus Expectant Management
MREC	Medical Research and Ethics Committee
NICE	National Institute for Health and Care Excellence
NVIUP	Non- viable Intra Uterine Pregnancy
POA	Period of Amenorrhea
PPUL	Persistent Pregnancy of Unknown Location

PUL	Pregnancy of Unknown Location
RCOG	Royal College of Obstetricians and Gynaecologist
SD	Standard Deviation
SPSS	Statistics Programmed for Social Sciences
TAS	Trans Abdominal Ultrasound
TVS	Trans Vaginal Ultrasound
UK	United Kingdom
UPT	Urine Pregnancy Test

DEFINITION OF OPERATIONAL TERMS

- i. *Gravida* refers to the number of pregnancies a woman has had regardless of the pregnancy outcome.
- ii. *Parity* refers to the number of pregnancies reaching viable gestational age (including live births and stillbirths). Viable gestational age varies from region to region. In Malaysia particularly, the viable gestational age is taken from 22 weeks of gestation onwards or if the gestation is unknown, the fetus is estimated to be more than or equal to 500gm.
- iii. *Primigravida* defines a woman as being pregnant for the first time.
- iv. *Multipara* defines a woman who has delivered two or more live births and stillbirths more than 22 weeks of gestation
- v. *Grandmultipara* defines a woman who has delivered five or more live births and stillbirths more than 22 weeks of gestation
- vi. *Gestational age* was estimated from the date of the last menstrual period and amended using ultrasonography in some women who were unsure of dates
- vii. *Pregnancy of unknown location* is a clinical scenario where the urine pregnancy test is positive but the location of the pregnancy cannot be visualized by TVS
- viii. *Intrauterine pregnancy* is defined as the pregnancy located inside the womb with evidence of a gestational sac that contains a fetal pole or yolk sac
- ix. *Ectopic pregnancy* is defined as the pregnancy that occurs outside of the womb, usually in one of the fallopian tubes. Fallopian tubes are the tubes connecting the ovaries to the womb
- x. *Failed pregnancy* is defined as a pregnancy that will not carry through to the term. It is also known as miscarriage

- xi. *Serum* refers to the clear, yellowish fluid that remains from blood plasma after clotting factors have been removed by clot formation
- xii. *Laparoscopy* is defined as a procedure that uses a laparoscope inserted through the abdominal wall to examine the inside of the abdomen
- xiii. *Salpingectomy* is defined as the surgical removal of a fallopian tube
- xiv. *Laparotomy* is defined as a surgical incision made in the wall of the abdomen into the abdominal cavity
- xv. *The pseudo gestational sac* is defined as a small amount of intrauterine fluid in a positive urine pregnancy test
- xvi. *The embryo* is defined as the early stage of development of a fertilized egg
- xvii. *Methotrexate* is a chemotherapy agent and immune system suppressant. It is used to treat cancer, autoimmune diseases, and ectopic pregnancy.
- xviii. *Free fluid* is defined as free intra-abdominal fluid. It may be seen in small volumes in female patients, particularly around the time of menses.

ABSTRAK

Objektif: Untuk mengetahui kelaziman dan hasil akhir dari kandungan yang tidak diketahui lokasinya di Hospital Raja Perempuan Zainab II (HRPZ II) bermula dari bulan Januari 2015 sehingga Disember 2019.

Rekabentuk kajian: Kajian ini merupakan kajian retrospektif yang dilakukan di Hospital Raja Perempuan Zainab II (HRPZ II). Rekod perubatan dari 150 wanita yg mengandung tetapi tidak diketahui lokasinya dan dimasukkan ke wad ginekologi bermula dari 1 Januari 2015 sehingga 31 Disember 2019 dikenalpasti daripada pangkalan data hospital. Rekod ini disemak dan data demografi serta hasil akhir dari kandungan tersebut dikumpulkan.

Keputusan: Sepanjang tempoh kajian, sebanyak 343 pesakit dengan kandungan yang tidak diketahui dikenal pasti dan 150 daripadanya diambil sebagai peserta kajian. Kelaziman daripada kandungan yang tidak diketahui adalah sebanyak 0.5%. Peratusan ini dikira berdasarkan jumlah kelahiran di HRPZ II sepanjang tempoh 5 tahun. Lebih separuh daripada mereka adalah multipara (60%) dan 45.3% daripadanya adalah dari kumpulan umur 26-35 tahun. 42.7% daripada pesakit hadir pada usia kandungan 6-7 minggu. Separuh daripada mereka (46%) datang dengan simptom seperti pendarahan dari faraj dan kesakitan pada bahagian perut. Sebahagian daripada pesakit dengan kandungan di dalam rahim akan menunjukkan tanda- tanda seperti '*intradecidual sign, free fluid*' dan ketebalan pada dinding rahim melalui ujian gelombang bunyi dengan purata 12.97mm. daripada keseluruhan pesakit dengan kandungan yang tidak diketahui, 54.7% daripadanya adalah kegagalan kandungan manakala 29.3% kehamilan di dalam rahim dan 16% kehamilan di luar rahim. Kebanyakan

daripada pesakit dengan kehamilan di luar rahim akan menjalani pembedahan laparoskopik (83%) manakala selebihnya akan menerima Methotrexate. 82% daripada pesakit dengan kehamilan di dalam rahim dan kegagalan kehamilan akan meneruskan temu janji dalam tempoh satu hingga dua minggu bagi menentukan nasib daripada kandungannya.

Kesimpulan: Secara keseluruhan, hasil akhir daripada kajian kandungan yang tidak diketahui yang dijalankan di HRPZ II adalah standing dengan kajian yang dilakukan di pusat-pusat kajian lain. Amalan semasa perlu dikekalkan atau ditambah baik terutamanya berkaitan dengan dokumentasi yang teliti dan latihan di kalangan petugas junior untuk memberikan penjagaan yang baik untuk pesakit.

Kata kunci: Kandungan yang tidak diketahui lokasinya, kandungan luar rahim, kandungan yang tidak berhasil, kandungan di dalam rahim.

ABSTRACT

Objectives: To study the prevalence and clinical outcomes of pregnancy of unknown locations in HRPZ II from January 2015 until December 2019.

Study design: This retrospective study was carried out in Hospital Raja Perempuan Zainab II (HRPZ II). The hospital database identified the medical records of 150 patients with a pregnancy of unknown location (PUL). Data of the patient who was admitted to the gynecology ward from 1st January 2015 and 31st December 2019 were reviewed and demographic and outcome data were collected.

Results: During the study period, 343 patients with PUL were identified and 150 of them were included in the study. The prevalence of PUL in HRPZ II was 0.5% based on the total number of deliveries in the 5 years. More than half of them were multiparous (60%) and 45.3% of them were from the age group of 26-35 years old. 42.7% of the patient presented at their 6-7 weeks of gestation. Almost half of them (46%) presented with vaginal bleeding and abdominal pain symptoms. Most of the patients with intrauterine pregnancy (IUP) showed features of intradecidua sign, free fluid, and thickened endometrium with a mean of 12.97mm on ultrasound. Of all the PUL cases, 54.7% of them were failing pregnancy while IUP and EP account for 29.3% and 16% respectively. Most of the patients in the EP group underwent laparoscopy (83.3%) while the remaining received Methotrexate therapy. 82% of patients in both IUP and EP groups attended follow-up in one to two weeks to confirm the pregnancy and there were no cases of EP noted.

Conclusion: The overall outcome of PUL in HRPZ II is comparable to the studies done in other centers. Current practice needs to be maintained or improved, especially regarding meticulous documentation and training of junior medical officers to provide the best care for the patients.

Keywords: Pregnancy of unknown location, ectopic pregnancy, failing pregnancy, intrauterine pregnancy

1.0 INTRODUCTION

Pregnancy of unknown location (PUL) is a common problem in early pregnancy. It is a clinical scenario when a urinary pregnancy test is positive but neither an intrauterine pregnancy (IUP) nor extra-uterine pregnancy can be visualized on transvaginal ultrasound (TVS). The incidence of PUL depends on the quality of ultrasound in a unit and has been reported to be between 8 and 31% (Bobdiwala S et al, 2016).

Due to a lack of standardized protocols, the management of PUL varies and may be stressful for women who are often subjected to repeated blood tests and scans before the outcome of the pregnancy is known. In general, research in this field has focused on identifying a test that enables clinicians to identify ectopic pregnancies (EP) within the overall population of PUL. Another research purpose was to reduce the number and length of follow-ups in women with PUL (Kirk E et al, 2009).

The outcome in women which initially classified as a PUL is as follows: intrauterine pregnancy (IUP – this can either be viable (VIUP) or non-viable (NVIUP), failed PUL (FPUL), ectopic pregnancy (EP), and persistent PUL (PPUL) (Bobdiwala S et al, 2016).

The different centers used different protocols in managing pregnancy of unknown locations to detect ectopic pregnancy. These protocols have their benefit. Therefore, proper management and intervention for the patient can be carried out. This study aimed to evaluate the outcome and current management of pregnancy in unknown locations.

2.0 LITERATURE REVIEW

2.1 PREGNANCY OF UNKNOWN LOCATION

Pregnancy of unknown location (PUL) is used when there is no sign of intra or extrauterine pregnancy or retained products of conception on transvaginal ultrasound (TVS) despite a positive pregnancy test (Bobdiwala S et al, 2016).

Whenever a woman presents with a positive pregnancy test but no evidence of pregnancy on TVS, clinical assessment, and serum beta-human chorionic gonadotropin (hCG) estimation should be carried out³. It is rare for women to be pregnant without positive hCG. The potential but rarer causes like posterior cranial fossa germ cell tumors and placental trophoblastic tumors must be considered though serum hCG will be high in these conditions (Sagili H et al, 2008)

The four possible outcomes of PUL are failing PUL, IUP, ectopic pregnancy (EP), and persisting PUL. The most common outcome is failing PUL (44-69%) which resolves spontaneously and can be either intra or extrauterine (Sagili H et al, 2008).

2.1.1.1 hCG and ultrasound

The concept of combining ultrasound with serum hCG using a discriminatory zone has been widely evaluated. It refers to a defined level of hCG above which the gestational sac of an intrauterine pregnancy should be visible on ultrasound with sensitivity approaching 100%. The current recommended value ranges from 1000–2400 iu/l. (Sagili H et al, 2008). For specialized

units performing high-resolution vaginal ultrasounds with prior knowledge of the woman's symptoms and serum hCG, a discriminatory zone of 1000IU/L can be used. However, the American Fertility Society suggested that the level should be around 2400IU/L (Karanth K L et al, 2010).

In multiple pregnancies, hCG levels should be interpreted with caution as they are a little higher, requiring an extra 2 or 3 days for the sacs to become visible. The possibility of a heterotopic pregnancy should also be considered in the differential diagnosis.

In women with a hCG result above the discriminatory level but no intrauterine gestational sac on ultrasound, steps must be taken to determine whether the pregnancy is ectopic. TVS must be performed meticulously because of potential pitfalls in image interpretation, considerable expertise is necessary (Sagili H et al, 2008).

Ideally, the discriminatory level for each test should be set by each institution based on that hospital's success in correctly identifying ectopic pregnancy. This variation depends on three factors, serum hCG assay techniques in use, quality of ultrasound equipment, and the operator experience (Karanth K L et al, 2010).

Setting a high discriminatory level minimizes the risk of intervening inappropriately before an intrauterine pregnancy has become apparent but at the expense of delaying the diagnosis of ectopic pregnancy by a few days (Sagili H et al, 2008).

In clinical practice, women with PUL may undergo unnecessary surgical procedures (laparoscopy) in those found to be having intrauterine pregnancy (IUP) or failing PUL and

subsequently fail to diagnose ectopic pregnancy. Studies have also shown that more than 50% of ectopic pregnancies in the PUL group have initial serum hCG levels below the discriminatory level (Karanth K L et al, 2010).

2.1.1.2 hCG pattern after 48 hours

The pattern of rising or fall in hCG after 48 hours and the hCG ratio is useful in distinguishing between PULs that will develop into failing PULs from intrauterine and ectopic pregnancy. This is particularly the case whenever the hCG levels are lower than the discriminatory zone or when an ultrasound diagnosis cannot be made despite the hCG being above the discriminatory zone (Sagili H et al, 2008).

The concept of the minimal rate of increase of hCG for an IUP of 66% in 48 hours was first reported in 20 women using an 85% confidence interval with a positive predictive value of 96.5%. However, 13–21% of ectopic pregnancies have an hCG rise that mimics an IUP. Although a doubling of hCG is often expected in 48 hours, this varies with gestation; as pregnancy progresses, doubling time lengthens. Intervention for an hCG rise of less than 66% over 2 days would potentially result in the interruption of viable pregnancies (Karanth K L et al, 2010).

Recent studies have attempted to redefine the hCG values to reduce unnecessary intervention. Based on observations in 287 women, the minimum rise for a potentially viable pregnancy in symptomatic PUL women was 53% at 2 days (99% confidence interval [CI]) but there was a lower cut off (35% increase over 2 days) for intrauterine pregnancy (99.9% CI) in a cohort study of 1249 women (Sagili H et al, 2008).

If hCG levels fall by at least 15%, the most likely outcome is failing PUL, although 8% of ectopic pregnancies have a fall in hCG similar to a spontaneous miscarriage and a higher cut off value of 21–35% (90% CI) has been mentioned in another study. When the rise or the fall in hCG is suboptimal, the most likely outcome is ectopic pregnancy. Approximately 71% of women with ectopic pregnancy have a rise in hCG that is slower than the minimal rise for a viable pregnancy or a decline that is slower than the minimal rate of fall in spontaneous miscarriage. A suboptimal rise in serum hCG predicts ectopic pregnancy with a positive predictive value of 43.5%. However, failing PULs and 15% of normal pregnancies will have an abnormal doubling time (Sagili H et al, 2008).

2.1.2 INTRAUTERINE PREGNANCY

IUP is defined when there is an intrauterine gestational sac seen on the scan and viable IUP is when an intrauterine gestational sac containing an embryo with a heartbeat has been visualized (Banerjee S, 2001). If an ultrasound scan shows a pregnancy of unknown viability, this may be an early viable pregnancy or a slow-growing pregnancy that is destined to miscarry (Al- Memar M et al, 2015).

In PUL, TVS is done to look for findings indicative of intrauterine or ectopic pregnancy. An intrauterine gestational sac is usually visible between 4¹/₂ and 5 weeks during endometrial cavity evaluation. The yolk sac appears between 5 and 6 weeks, and a fetal pole with cardiac activity is first detected at 5¹/₂ to 6 weeks. With transabdominal sonography, these structures are visualized slightly later (Cunningham F et al, 2014).

In contrast, with ectopic pregnancy, a trilaminar endometrial pattern can be diagnostic. Its specificity is 94%, but with a sensitivity of only 38%. In addition, Moschos and Twickler (2008) determined that in a woman with PUL at presentation, no normal pregnancies had a stripe thickness <8mm (Cunningham F et al, 2014).

Anechoic fluid collections, which might normally suggest an early intrauterine gestational sac, may also be seen with ectopic pregnancy. These include pseudogestational sac and decidual cyst. First, a pseudo sac is a fluid collection between the endometrial layers and conforms to the cavity shape. If a pseudo sac is noted, the risk of ectopic pregnancy is increased. Second, a decidua cyst is identified as an anechoic area lying within the endometrium but remote from the canal and often at the endometrial-myometrial border (Cunningham F et al, 2014). Ackerman and colleagues (1993) suggested that this finding represents early decidual breakdown and precedes decidual cast formation.

These two findings contrast with the intradecidual sign seen within intrauterine pregnancy. This is an early gestational sac and is eccentrically located within one of the endometrial stripe layers. The American College of Obstetricians and Gynecologists 2011 advises caution in diagnosing a uterine pregnancy in the absence of a definite yolk sac or embryo (Cunningham F et al, 2014).

2.1.3 ECTOPIC PREGNANCY

An EP is any pregnancy implanted outside of the endometrial cavity and is potentially life-threatening (Al- Memar M et al, 2015). 6 maternal deaths were reported between 2006 and 2008. The fatality rate has decreased over recent years, suggesting that earlier diagnosis and treatment may have made an impact (Elson C J et al, 2016).

Risk factors for ectopic pregnancy include tubal damage following surgery or infection, smoking, previous ectopic pregnancy, and in vitro fertilization. However, the majority of women with ectopic pregnancies have no identifiable risk factor (Al- Memar M et al, 2015).

TVS is now the gold standard technique for the diagnosis of ectopic pregnancy. Using this approach, over 70% of ectopic pregnancies may be diagnosed at the time of presentation and over 90% may be visualized once follow-up scans have been performed (Al- Memar M et al, 2015). The diagnosis of ectopic pregnancy should be based on the identification of an extrauterine sac and complex adnexal mass or echogenic fluid rather than failing to demonstrate intrauterine pregnancy (Sagili H et al, 2008).

The sonographic diagnosis of ectopic pregnancy rests on the visualization of an adnexal mass separate from the ovary. If fallopian tubes and ovaries are visualized and an extrauterine yolk sac, embryo, or fetus is identified, then an ectopic pregnancy is confirmed. In other cases, a hyperechoic halo or tubal ring surrounding an anechoic sac can be seen. Alternatively, an inhomogeneous complex adnexal mass is usually caused by a hemorrhage within the ectopic sac or by an ectopic pregnancy that has ruptured into the tube (Cunningham F et al, 2014).

Overall, approximately 60% of ectopic pregnancies are seen as an inhomogeneous mass adjacent to the ovary; 20% appear as a hyperechoic ring; and 13% have an obvious gestational sac with a fetal pole. Importantly not all adnexal masses represent an ectopic pregnancy, and integration of sonographic findings with other clinical information is necessary (Cunningham F et al, 2014).

Placental blood flow within the periphery of the complex adnexal mass, the ring of fire can be seen with transvaginal colour doppler imaging. Although this can aid in the diagnosis, these findings can also be seen with a corpus luteum of pregnancy, and differentiation can be challenging (Cunningham F et al, 2014).

In women with suspected ectopic pregnancy, evaluation for hemoperitoneum can add valuable clinical information. Sonographically, the hemoperitoneum is anechoic or hypoechoic fluid. Blood initially collects in the dependent retro uterine cul-de-sac, and then additionally surrounds the uterus as it fills the pelvis. As little as 50ml can be seen in the cul-de-sac using TVS and transabdominal imaging helps to assess the hemoperitoneum extent. Free fluid in the pericolic gutters and Morison pouch is not seen until accumulated blood reaches 400 to 700ml. Peritoneal fluid in conjunction with an adnexal mass is highly predictive of ectopic pregnancy. However, a small amount of peritoneal fluid is physiologically normal (Cunningham F et al, 2014).

Surgical management (laparoscopy/laparotomy) is indicated if the woman is symptomatic (either at presentation or during conservative management) or if an ectopic pregnancy is

visualized Some early ongoing and self-limiting ectopic pregnancies are too small to be seen, thus resulting in false-negative laparoscopies. Laparoscopy has a false negative rate of 3–4% (if done too early) and a false positive rate of 5% (because of retrograde uterine bleeding) (Sagili H et al, 2008).

2.1.4 FAILING PREGNANCY

Failing pregnancy is a pregnancy that is resolved spontaneously and can be either intrauterine or extrauterine pregnancy (never located in the TVS). It contributes to 50-70% of PUL and on expectant management resolves spontaneously. Serum progesterone at presentation will be <20nmol/l and serum hCG level at 0, 48 hours continue to fall >15%. Weekly hCG monitoring is necessary till < 10 IU/L. Follow-up with TVS is not mandatory (Sagili H et al, 2008).

2.1.5 PERSISTING PUL

Persisting PUL are defined as those in which serum hCG levels fail to decline, there is no evidence of trophoblastic disease and the location of pregnancy cannot be identified using transvaginal ultrasound or laparoscopy. Usually, the serum levels of hCG are low (500 IU/l) and have reached a plateau (doubling time of 7 days or more). This subset accounts for approximately 2% of the total number of PUL (Sagili H et al, 2008).

2.1.6 PREVALENCE OF PREGNANCY OF UNKNOWN LOCATION

The prevalence of PUL is influenced by the experience of the sonologist and the quality of sonology used in the specialized scanning units, the overall incidence of pregnancy of unknown locations is as low as 8 -10% (Karanth K L et al, 2010).

A paper by Sagili H and Mohamed K (2008) also concluded that a lower incidence of PUL (8-10%) was observed in a specialized scanning unit. It also stated that the sonographer's experience influences the prevalence of PUL.

Based on NICE clinical guidelines on Pregnancy of Unknown Location (June 2020), PUL occurs in up to 30% of initial early pregnancy scans.

2.1.7 PREVALENCE OF ECTOPIC PREGNANCY

A study that was conducted by Karants K L et al, 2010 regarding pregnancy of unknown location in Melaka Manipal Medical College Malaysia, stated that the prevalence of early EP in the PUL population is 8.1-42.8% in non-specialized scan centers whereas in specialized scan centers is 8.1- 14%. The accuracy of diagnosis by the specialist center is 87- 93%. The only portion of PULs in specialized scan centers represents high-risk ectopic pregnancy (Banerjee S et al, 2001).

Fistouris J et al (2016) conducted a retrospective comparative study in 2016 to classify the PUL according to four different hCG protocols and found out that the prevalence of EP among PUL

was reported to be between 6 and 17 % which reflects the frequency of EPs missed on the initial TVS.

Clinical research on the role of ultrasound in diagnosing and managing early pregnancy complications by Al-Memar M et al (2015) concluded that the number of ectopic pregnancies in women classified as having PUL varies and rates range from 7% to over 30% (Al- Memar M, 2015).

Young L et al, 2019 conducted a study on the clinical outcome of pregnancies of unknown locations, an audit of 112 cases in New Zealand. This study showed that PUL continues to be a challenging and resource-intensive clinical scenario. The rate of undiagnosed EP requiring intervention is around 10%, and the probability that a PUL represents a small non-visualized ongoing IUP is relatively low (15%).

2.1.8 OUTCOME OF PREGNANCY OF UNKNOWN LOCATION

PUL can lead to serious complications such as ruptured ectopic pregnancy. A study conducted by Amer N et al (2015) in Saudi Arabia showed that the management of choice for asymptomatic patients having a pregnancy of unknown location is expectant. The study also concluded that most of the patients with persistent pregnancy of unknown location and ectopic pregnancy can be managed medically.

Another paper was published by Zubair S et al (2017) in the United Arab Emirates regarding the outcome of pregnancies of unknown location revealed that only 6% of patients were diagnosed with a pregnancy of unknown location. Furthermore, after they stratify concerning medical history, duration of disease, symptoms, parity, and age, significant differences were observed between the occurrences of various pregnancy outcomes for symptoms only.

A prospective study by Sri A et al (2017) regarding the outcome of pregnancy of unknown location in India concludes that management of choice for asymptomatic patients having pregnancy of unknown location is expectant management. Most of the patients suspected to have PUL resolved into failed PUL (48.83%) or IUP (36.04%). 9.3% were diagnosed with EP while 5.81% had persistent PUL.

A retrospective study was conducted by Thida W et al (2016) in the United Kingdom. They review the outcome and management of PUL and reveal the PUL rate in their unit is 9% which is similar to the reported rate in the literature. The predicted outcomes like failing pregnancy, ectopic pregnancy, IUP, and persistent PUL are comparable to those reported. The majority of the outcome of PUL is not ectopic. The study also said that further management of each outcome of PUL should be based upon good history taking, clinical assessments, hemodynamic stability, and patient's informed choices.

Young L and Necas M conducted a study on The clinical outcome of pregnancies of unknown location: an audit of 112 cases and concluded that out of 585 women that were referred for suspicion of EP, 19% were categorized as PUL. The final outcomes in these women were

complete miscarriage (52%), IUP (13%), presumed EP (11%), incomplete miscarriage (11%), confirmed EP (10%), and molar pregnancy (2%).

2.2 STUDY JUSTIFICATION

The pregnant woman presents a diagnostic challenge as physiological, anatomical, and biochemical changes of pregnancy may mask symptoms and signs, as well as the pregnancy itself being the source of the problem. Early pregnancy complications are one of the commonest problems involving reproductive-age women.

In this new era of technology, ultrasound and transvaginal probe are mostly available in the government clinic or even in the general practitioner clinic. Thus, the regular usage of transvaginal sonography has led to the diagnosis of early pregnancy complications, sometimes as early as 4 weeks gestation. This has resulted in more women presenting at early gestation and being diagnosed with a pregnancy of unknown location. Thus, this study was conducted to evaluate the prevalence of ectopic pregnancy as well as the outcome of pregnancy of unknown location in HRPZ II from January 2015 until December 2019.

3.0 OBJECTIVES

GENERAL OBJECTIVE

To study the prevalence and clinical outcomes of pregnancy of unknown locations in HRPZ II from January 2015 until December 2019

SPECIFIC OBJECTIVES

1. To determine the prevalence of ectopic pregnancy from a pregnancy of unknown location.
2. To determine the clinical outcomes of pregnancy of unknown location which are ectopic pregnancy, intrauterine pregnancy, or failing pregnancy.
3. To determine the treatment options for pregnancy of unknown location.

4. METHODOLOGY

STUDY DESIGN

A retrospective study.

STUDY LOCATION

This study was conducted in HRPZ II. The relevant information of the patients was extracted at the Medical Record Unit, HRPZ II.

STUDY DURATION

The study duration was from the 1st of January 2015 until 31st of December 2019. The period of data collection was from the 1st of March 2020 until 30th of June 2020.

REFERENCE POPULATION

The reference population for this study was all pregnant women who were admitted to gynecology ward HRPZ II from 1st of January 2015 until 31st December 2019 with early pregnancy complications.

SOURCE POPULATION

The source population for this study was all pregnant women who were diagnosed with a pregnancy of unknown location after transvaginal sonography and they were admitted to HRPZ II from 1st of January 2015 until 31st December 2019 for further evaluation and intervention.

STUDY PARTICIPANTS

150 pregnant women who were diagnosed with a pregnancy of unknown location in gynecology ward HRPZ II from 1st of January 2015 until 31st December 2019 and fulfilled the inclusion and exclusion criteria have been selected in this study.

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

All women who were admitted for pregnancy of unknown location in HRPZ II from 1st of January 2015 until 31st December 2019.

EXCLUSION CRITERIA

Patients with incomplete data

SAMPLE SIZE AND SAMPLING METHOD

Sample size (n) was calculated using the single population proportion formula

Calculation by using confident interval (CI) 95% and 5% precision

$$n = \left(\frac{z}{\Delta}\right)^2 p(1 - p)$$

p = expected proportion of individuals in the sample with the characteristics of interest at the determined 100 (1- α) % confidence interval. It can be obtained from literature or a pilot study or preliminary work

Δ = precision

$Z = 1.96$

Sample size calculation based on the prevalence of ectopic pregnancy.

According to the study by Young L et al, 2019; the clinical outcome of pregnancies of unknown location, an audit of 112 cases in New Zealand showed that PUL continues to be a challenging and resource-intensive clinical scenario where the rate of undiagnosed ectopic pregnancy requires intervention is around 10%

$$n = \left(\frac{1.96}{0.05}\right)^2 0.1(1 - 0.1) = 137$$

The estimated sample was 137

Sample size calculation based on the prevalence of pregnancy of unknown locations.

In a study conducted by Karanth K L et al, 2010 regarding pregnancy of unknown location, in Melaka Manipal Medical College Malaysia, the overall incidence of pregnancy of unknown location is as low as 8-10%. So the estimated sample size calculated using the single population proportion formula is also 137.

Thus, the sample size determination based on the prevalence of ectopic pregnancy was chosen.

$$\text{Sample size} = 137 + 10\% (\text{dropouts}) = 150$$

METHOD OF DATA COLLECTION

The data were derived from a retrospective case review of 343 patients who were referred for pregnancy of unknown location to HRPZ II from 2015 to 2019. The cases were identified based on the admission book in the gynecology ward with the diagnosis on admission including pregnancy of unknown location or to rule out ectopic pregnancy. Further information on the cases was further retrieved from the computer-generated SPP (Sistem Pengurusan Pesakit) based on the registration number or identification certificate. If the information needed is incomplete or not available, the patient's folder then been traced from the medical record unit. However, if the data is still incomplete, it is considered 'missing' and subjected to drop out.

STUDY METHOD

A total of 150 patients who were admitted to HRPZ II between 2015 and 2019 and fulfilled the criteria were studied retrospectively. All patients were initially referred from an emergency

department, health clinic, district hospital, or general practitioner with a diagnosis of PUL. They presented earlier with a positive pregnancy test but were unable to determine the location of the pregnancy. Some of them complained of abdominal pain or minimal per vaginal bleeding, but some of them were asymptomatic. They were reviewed by the Obstetric & Gynaecology team on the same day of referral.

Gynecological examination and TVS were performed on all of them. If the assessor was unable to further determine the exact location of the pregnancy, 0 hours and 48-hour serum hCG were collected, but only in a stable patient. If the level increased up to 66%, it was likely IUP. If the level decreased at least 15%, the most likely outcome was failing PUL. Ectopic pregnancy was diagnosed when the increment or decrement of serum hCG was suboptimal.

IUP patients were given further follow-up in EPAU (Early Pregnancy Assessment Unit) in 2 weeks to confirm the pregnancy by TAS. As well as in the failing PUL patients, were given follow-up in 2 weeks to repeat TAS/TVS and a urine pregnancy test to confirm the pregnancy was failing.

In ectopic pregnancy patients, they were treated either with surgical intervention or medical treatment. Some of them underwent laparoscopic and unilateral salpingectomy but some of them were subjected to medical treatment; intramuscular methotrexate according to the protocol. Thus this study aims to further evaluate the outcome of the PUL.

DATA COLLECTION

The data was collected in 6 categories, which include:

1. Patient's demographic data which includes age, gravida, parity, last normal menstrual period, gestational age, date of first scan (TVS) together with the indication for a scan as well as scan findings.
2. Biochemistry at presentation including date, time, and value for serum hCG level at presentation (0 hours).
3. Biochemistry at 48 hours including date, time, and serum hCG level and reason for not doing the 48-hour blood.
4. Triage is based on the increment or decrement of serum hCG whether to fall under ectopic pregnancy, intrauterine pregnancy, or failing pregnancy.
5. Further information regarding intrauterine and failing pregnancy, symptoms, repeated scan, and urine pregnancy test on follow-up.
6. Intervention information and the outcome after the intervention
7. Follow-up information for intrauterine and failing pregnancy.

Details of each case were recorded using the DATA COLLECTION SHEET.

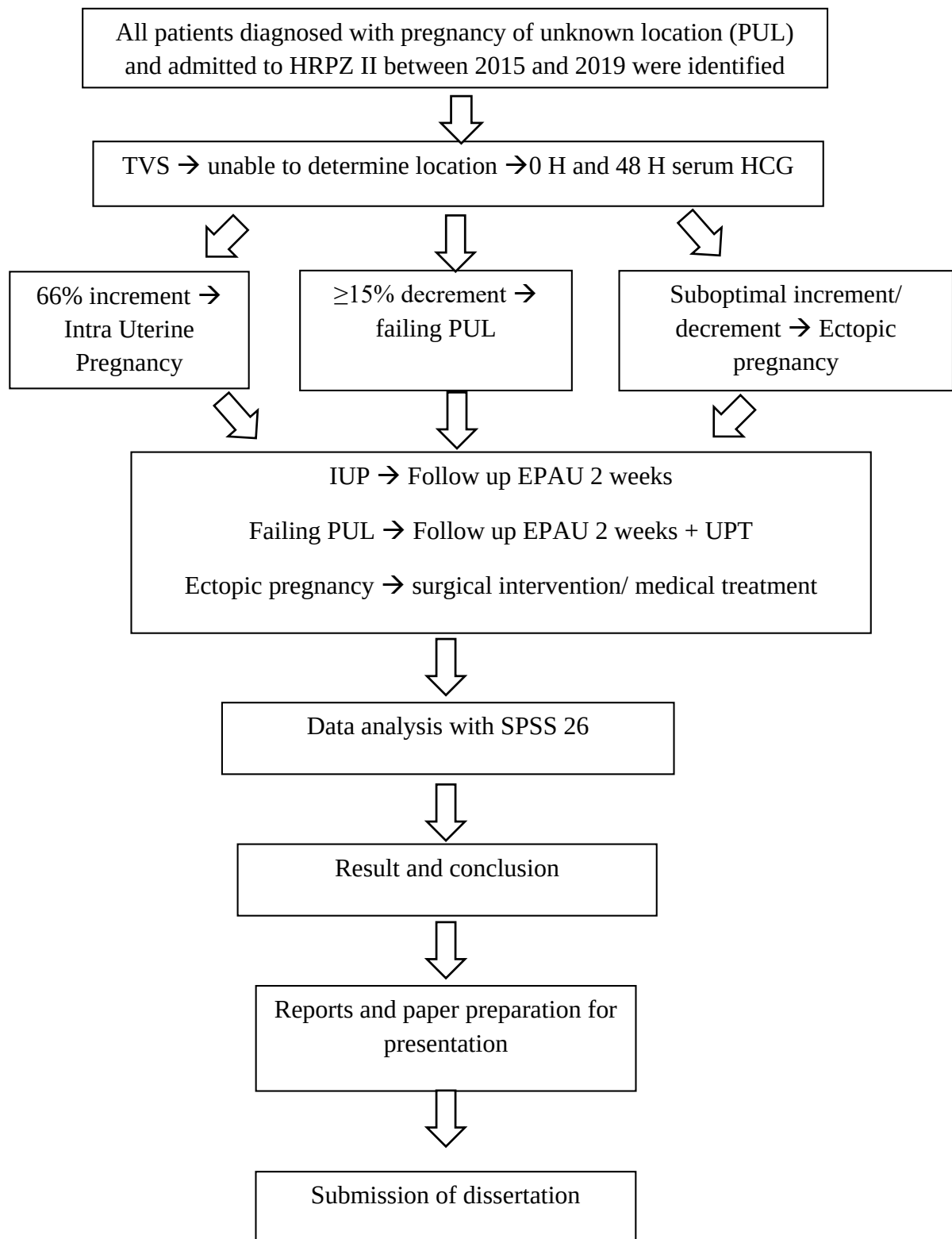
STATISTICAL ANALYSIS

Statistics programmed for social sciences (SPSS) software (version 26) was used for data processing and analysis. Descriptive statistics were utilized in which categorical data will be described as a percentage whereas continuous data will be described as mean (sd).

ETHICAL ISSUE

This study was conducted with strict adherence to ethical considerations. An ethical clearance approval was obtained from the Jawatankuasa Etika Penyelidikan (Manusia), JEPeM- USM, and the Ministry of Health's Medical Research and Ethics Committee (MREC). An approval letter as permission to conduct this study was obtained from the director of Hospital Raja Perempuan Zainab II. All the information retrieved from the medical records remained confidential. No individual names were used and cases were coded accordingly.

FLOW CHART OF THE STUDY



RESULTS AND ANALYSIS

During 5 years study period (1st of January 2015 until 31st December 2019), there were summations of 63 923 deliveries in HRPZ II. A total of 343 patients with PUL were reviewed but only 150 of them fulfilled the inclusion and exclusion criteria and thus included in this study. The prevalence of PUL cases was calculated based on the total number of deliveries in HRPZ II as we do not have the data on the total number of patients with early pregnancy complications. Thus the prevalence of PUL was 0.5%. The data obtained were expressed as mean (SD- standard deviation) for numerical and n= frequency (%) for categorical variables as tabulated in Table 1.

Table 1: Socio-demographic characteristics of patients

Variables	N (%); n =150
Age (years)	
< 18	8 (5.3)
18-25	33 (22.0)
26-35	68 (45.3)
36-45	41(27.3)
Gravida	
1 (primigravida)	43 (28.7)
2-5 (multigravida)	90 (60.0)
>5 (grand multigravida)	17 (11.3)

Parity	
Nulliparous	54 (36.0)
Parous	96 (64.0)
Gestational age at presentation (weeks)	
4-5	28 (18.7)
6-7	64 (42.7)
8-9	17 (11.3)
>9	10 (6.7)
Uncertain	31 (20.7)
Indication for scan	
Bleeding and pain	69 (46.0)
Bleeding only	35 (23.3)
Pain only	32 (21.3)
Amenorrhea	14 (9.3)

The results from the data showed that the majority of the patients were between the age of 26- and 35 years old, 68 (45.3%), followed by 36-45 years old; 41(27.3%). A small percentage of them are below the age of 18 years old; 8(5.3%) and the rest from the age 18-25 years old; 33(22%).