A REVIEW OF INTRA-UTERINE DEATH FROM 2013 TILL 2017 IN HOSPITAL UNIVERSITI SAINS MALAYSIA, KUBANG KERIAN, KELANTAN

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Aashreena Randhawa a/p Mohinder Singh

1.3 LIST OF ABBREVIATION

IUD	Intrauterine Death
ELLSCS	Elective Lower Segment Cesarean Section
EMLSCS	Emergency Lower Segment Cesarean Section
HUSM	Hospital Universiti Sains Malaysia
JEPeM	Jawatankuasa Etika Penyelidikan (Manusia) USM
USM	Universiti Sains Malaysia
BMI	Body Mass Index
MDG	Millennium Development Goals
TORCHES	Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes Simplex Virus
WHO	World Health Organization

1.4 LIST OF TABLES

1.5 ABSTRACT

OBJECTIVE: Retrospective review of intrauterine death in Hospital Universiti Sains Malaysia (USM) from 1st of January 2013 until 31st of December 2017. The current study aims to look at the causes and factors associated with intrauterine death (IUD) in a teaching hospital from the1st of January 2013 until the 31st of December 2017.

STUDY METHOD: This retrospective study involved 174 patients. All mothers who presented with IUD occurring after 22 weeks of period of amenorrhea and gestation in Hospital USM from 1st of January 2013 until 31st of December 2017 were included. Social demographic data of the mothers were collected and data were reviewed for causes and risk factors associated with IUD.

RESULT: Mothers in the age group of 25 till 29 years old had the highest number of IUD at 31 % (n=54) with primigravida's recording the highest number of IUD at 41.95 % (n= 73). The main causes which lead to IUD were infection (n=58) 33.3 %, unexplained causes (n=47) 27.7 % ,congenital anomalies (n=45) 25.9% , placental abruption (n=15) 8.62% and trauma (n=9) 5.2% The risk factor associated with IUD in this study were pre-gestational / gestational diabetes mellitus at 25.86 % (n=45) , hypertensive disease 14.4% (n=25) , history of previous IUD 11.5% (n=20) and other medical illnesses 2.3% (n=4).

CONCLUSION: CONCLUSION: The current study suggests that in the past 5 years, the main causes of IUD in Hospital USM include infections, congenital anomalies, and unexplained causes. Mothers with GDM or diabetes carry a higher risk.

ABSTRAK

OBJEKTIF : Kajian retrospektif ini dijalankan untuk menganalisis kejadian kematian dalam kandungan yang berlaku di Hospital Universiti Sains Malaysia bagi tempoh masa dari 1 Januari 2013 hingga 31 Disember 2017. Di samping itu, kajian ini turut dijalankan bagi menentukan sebab dan faktor risiko yang menyebabkan kejadian kematian dalam kandungan di kalangan ibu-ibu yang telah mendapatkan rawatan di hospital ini bagi tempoh masa yang sama.

KAEDAH KAJIAN: Kajian yang dijalankan secara retrospektif ini melibatkan 174 ibu-ibu**.** Kesemua data yang diperoleh adalah berkaitan ibu-ibu yang telah disahkan hamil bagi jangka masa 22 minggu dan ke atas dan telah dirujuk ke Hospital Universiti Sains Malaysia bagi tempoh masa dari 1 Januari 2013 hingga 31 Disember 2017. Data demografi sosial ibu-ibu telah dikumpul dan dianalisa bagi mengkaji punca dan faktor risiko yang telah menyebabkan kematian dalam kandungan.

KEPUTUSAN: Ibu-ibu yang berada dalam lingkungan usia 25 hingga 29 tahun merupakan catatan golongan tertinggi (n=54) yang menyumbang kepada kadar kematian dalam kandungan dengan peratusan 31%. Ibu-ibu yang hamil buat kali pertama merupakan kumpulan paling ramai yang mengalami kematian dalam kandungan iaitu sebanyak 41.95% (n = 73). Faktor utama yang menyebabkan kematian dalam kandungan adalah berpunca daripada jangkitan kuman iaitu (n=58) 33.3%, punca yang tidak dapat dikenal pasti (n=47) iaitu 27.7% dan anomali kongenital sebanyak (n=45) 25.9%, *'abruptio placenta'* (n=15) 8.62% dan kecederaan

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seramai 9 orang ibu, 5.2%. Faktor risiko yang dikaitkan dengan kematian dalam kandungan adalah apabila para ibu mempunyai penyakit kencing manis dalam kehamilan atau sebelum kehamilan (n=45) 25.86%, diikuti dengan penyakit darah tinggi dalam kandungan atau sebelum kehamilan (n=25) 14.3% , para ibu yang sudah memiliki sejarah kematian dalam kandungan (n=20) 11.5% dan penyakit lain-lain (n=4) 2.3% .

KESIMPULAN : Menerusi kajian yang telah dijalankan di Hospital USM, penyebab utama yang menyumbang ke kematian bayi dalam kandungan disebabkan infeksi, kelainan kongenital dan sebab-sebab yang tidak dikenal pasti. Para ibu yang menghidapi kencing manis sama ada sebelum atau sewaktu mengandung mempunyai risiko yang lebih tinggi.

2.0 INTRODUCTION AND LITERATURE REVIEW

According to the International Classification of Diseases, revision 10(ICD-10), an early fetal death is the death of a fetus weighing at least 500gm (or if birthweight is unavailable then after 22 weeks of gestation or with a crown-heel length of 25cm or more). A late fetal death is defined as the death of a fetus weighing at least 1000gm or a gestational age of 28 weeks or a crown heel length of 35cm or more[1].

The World Health Organization (WHO) defines fetal death, according to the International Statistical Classification of Diseases and Related Health Problems – 10th Revision (ICD-10) [2,3] and this has been adopted by our country. The National Obstetrics Registry 4th report published for data between 2013-2015 follows the WHO recommendation and covers all IUD delivered weighing 500gm with a corresponding gestational age of 22 weeks. From the Malaysian Health facts, it was reported that stillbirth rates in Malaysia was 4.4 per 1000 live births in 2015 and 4.3 per 1000 live births in 2014 & 2013 [4].

The moment of diagnosis is often a very painful event for the prospective parents, as well as for the person conveying the information.

It is one of the most stressful life events as the family's anticipation of a joyous birth is supplanted by sadness, despair, confusion, and loss, including loss of the desired child, loss of self-esteem as a parent, and loss of confidence in the ability to produce a healthy child.

Psychological sequelae include depression, post-traumatic stress disorder, and anxiety, which may adversely affect a subsequent pregnancy.

Intrauterine death has multifactorial etiologies and is a significant contributor to perinatal mortality in developing countries although improved care and advanced techniques of perinatal diagnosis have significantly reduced the incidence.

2.1 GLOBAL STATISTICS ON INTRAUTERINE FETAL DEATH

According to statistics by the World Health Organization (2015), approximately 2.6 million intrauterine deaths occur annually and 1.3 million occur during labour and birth, most result from preventable conditions[2,3].

The Lancet published "The Ending Preventable Stillbirths Series Study Group," which has helped to promote global public health efforts. The initial goal was to reduce the stillbirth rate to less than 15/1000. This has been achieved already in many industrialized countries; however, countries in Asia and Africa still have much higher rates of stillbirth attributed mainly to lack of access to healthcare providers [5]. In the sub-Saharan Africa , the stillbirth rate is 21.7 per 1000 livebirths[5]. Based on the latest statistics as of 2015, out of 2.6 million IUD occurring annually globally, 23.2% are from India.

Developing countries in South Asia and Sub Saharan Africa together constitute 70% of the world's IUD burden. In the southeast Asia region, Laos documented an estimated IUD rate of 23.7 per 1000 live births. By comparison, rates of 3-5 per 1000 deliveries have been documented in the U.S and other developed countries. For mid-level countries such as South and Central America, rates of 10-15 per 1000 were reported.

2.2 LOCAL STATISTICS ON INTRAUTERINE FETAL DEATH

In tandem with the World Health Organization's theme for 2016 'Making every baby count', the National Obstetrics Registry produced a report for 415 021 deliveries from 2013 until 2015. All data from 13 tertiary state hospitals and 1 hospital in federal territory, excluding all university hospitals were collected and reported [4].

The National Obstetric Registry in Malaysia (2015) reported a stillbirth rate of 4.4 per 1000 live births. In Peninsular Malaysia, the stillbirth rate was highest amongst Indians, recording a 10.73 stillbirth rate per 1000 live births. The Melanau ethnic has the highest stillbirth rate in Borneo Malaysia, which is 14.73 stillbirth rate per 1000 live births [4]. Based on the National Obstetric Registry 2016-2017, Hospital Raja Perempuan Zainab II, Kelantan reported a stillbirth rate of 5.84 (2016) and 7.7 (2017) per 1000 live births [6]. Table 1 shows the number of IUD in Hospital USM.

Table 1: Number of IUD , Livebirths and Prevalence in HUSM

Year	No. of IUD	Total Deliveries	Prevalence (%)
2013	74	6880	1.07
2014	68	8809	0.77
2015	76	9930	0.76
2016	56	9195	0.61
2017	61	7202	0.84

Rosnah Sutan [7] conducted a study based on existing, available information published from 1990 up to January 2007 on IUD in Malaysia. Malaysia has recorded a remarkable decrease in IUD rates in the early 1950s, which was about 28 per 1000 births. During the 1990s, this indicator was about 5 per 1000 births. However, this reduction was occurring at different rates in different geographical areas within the country because of the differences in inaccessibility to healthcare facilities. Intrauterine death rates increased in 1997 (6.6 per 1000 births) and decreased in 2000 (5.6 per 1000 births). The intrauterine death rate showed an increase in its rate in 1997 most likely due to the enforcement of the reporting system by the Family Health Division from the year 1997 [7].

2.3 CAUSES OF INTRAUTERINE DEATH

The fourth goal of the Millennium Development is to reduce mortality among children under 5 years old by two thirds between 1990 and 2015. Worldwide, child mortality between 1980 and 2000 was reduced by one third while the neonatal mortality rate was reduced only by a quarter. To achieve MDG 4 goals, neonatal mortality must at least be halved. Neonatal mortality is divided into early and late neonatal death. Early neonatal deaths occur during the perinatal period, and the perinatal period is defined as completed 22 weeks of pregnancy and ends 7 days after birth [8].

2.3.1 Trauma

It is estimated that 10% to 69% of the women in the world experience some form of violence at the hands of their husbands or male partners. The prevalence of domestic violence among pregnant women in the US studies ranges from 1% to as high as 20% with most studies reporting a range of 4% to 8%. Based on a study done in Malawi between 2014 until 2015, 21 % of 792 women reported intimate physical violence during pregnancy. They were significantly more likely to have a history of adverse delivery outcomes in the unadjusted (prevalence ratio 1.23; 95% confidence interval 1.08–1.41) and adjusted (adjusted prevalence ratio 1.19; 95% CI 1.01–1.40) analyses [9]. There are several pathways on how domestic violence leads to IUD. One of it is the direct effect of blunt trauma and the resultant fetal death or subsequent pregnancy outcome. A second potential pathway is elevated stress levels and poor nutrition, both of which are associated with low birth weight or preterm delivery and are well-known risk factors for perinatal and infant mortality. A third possible pathway is the

deterrent effect of violence on women's use of preventive or curative health services during pregnancy.

Physical trauma is an important incidental cause of maternal and perinatal mortality. Motor vehicle accidents (MVA's) are the leading cause, and account for up to 80% of trauma in pregnancy, followed by falls and assaults. MVA in pregnancy is associated with a perinatal death rate of approximately between 3 and 6 per 100 000 live births in high-income countries [10].

2.3.2 Fetal Congenital Malformations

Fetal congenital malformations are amongst the important causes of intrauterine death and infant mortality and contribute to childhood morbidity. The number of birth defects in infants is increasing antenatally and during the neonatal period due to advanced diagnostic technology, especially the ultrasound.

In a population study performed in Britain in 5 different geographical regions from 1991 until 1999, the proportion of all intrauterine deaths due to congenital anomaly was 10.5 % [11].

2.3.3 Infection

Infection may cause intrauterine death in multiple mechanisms, including direct infection, placental damage, and severe maternal illness. A large variety of organisms have been associated with stillbirth, including many bacteria, viruses, and protozoa. In developed countries, between 10% to 25% of intrauterine deaths may be caused by an infection, whereas in developing countries, which often have higher intrauterine death rates, the contribution of infection is much greater . Based on a study conducted in 6 countries, which included India, Pakistan, Guatemala, Democratic republic of Congo, Zambia and Kenya to investigate the cause of intrauterine deaths through 2014 until the 31st of December 2015, 109 911 women

were enrolled and 2847 women experienced intrauterine death. The second commonest cause of IUD is an infection at 20.8% [12]. TORCHES is an acronym for Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes Simplex Virus. This investigation is taken in cases of recurrent miscarriages, intrauterine death, intrauterine growth restriction or congenital anomalies. It refers to a group of infectious agents having crossed the placenta during pregnancy. Most of these infections cause mild maternal morbidity, but serious fetal consequences. This group of infections causes hydrops fetalis, microcephaly, congenital heart disease, and intrauterine death. These organisms are transmitted due to lack of good hygienic conditions, contaminated blood, water and soil and airborne respiratory droplets. Thus, TORCH infections in pregnancy women are usually established by demonstration of sero-conversion in paired sera or by demonstration of specific Ig-M antibodies [13].

2.3.4 Placental Abruption

One of the common placental causes of IUD is placental abruption. If abruption occurs in a premature fetus, it is more likely to cause fetal death, and unfortunately, the rates appear to be increasing. The etiology of placental abruption can be due to underlying hypertensive disorder in pregnancy or due to sudden mechanical events such as blunt abdominal trauma. The immediate cause of premature placental abruption is the rupture of maternal vessels, either an artery or vein in the decidua basalis. This leads to the rapid development of potentially life-threatening scenarios such as maternal disseminated intravascular coagulation and intrauterine death.

A single-centre retrospective study was performed at a tertiary university in Karachi, Pakistan from January to June 2008. During that study period, there were a total of 1011 vaginal deliveries in the department, of which there were 100 fetal deaths. It was reported that 22% of the IUD was due to abruptio placenta [14].

2.3.5 Unexplained

Unexplained IUD is a difficult problem to study because of the paucity of clues. It cannot be attributed to an identifiable fetal, placental, or maternal cause mostly due to lack of information or because the cause cannot be determined at the current level of diagnostic ability. A publication in 2019 on a single-centre retrospective study carried out over a period of 12 months from January until December 2014 in a civil hospital in Nepal , there were 10245 total deliveries and 152 cases of intrauterine death. Out of 152 cases, 40 cases (26.3%) were unexplained causes [15].

2.4 RISK FACTORS OF INTRAUTERINE DEATH

Intrauterine death continues to pose a serious challenge worldwide, and more so in developing countries even though a significant decline has occurred in recent years. To prevent and reduce the numbers of IUD improved maternal health, and care during pregnancy is needed. Information regarding causation and risk factors is crucial.

2.4.1 Hypertensive Disease

Hypertensive disorders in pregnancy complicate 5-8% of pregnancies and are associated with increased perinatal morbidity and mortality alongside maternal morbidity. Pre-eclampsia, part of the spectrum of gestational hypertension, is typically a disease of first pregnancy, with a 1

reduction of incidence among multiparas. The occurrence of gestational hypertension in one pregnancy is a strong indicator of recurrence in the next pregnancy.

In a study conducted in India from August 2015 to February 2019 , there were a total of 46 816 deliveries at the institution and 1239 were IUD. Out of 1239 IUD, 304 mothers (24.9%) had hypertensive disease in pregnancy [16].

2.4.2 Pre-Gestational / Gestational Diabetes Mellitus

Population-based studies demonstrated a twofold to fivefold increase in the risk of IUD among women with pre-gestational diabetes. There are a wide variety of factors that lead to IUD in diabetic pregnancies. These include placental insufficiency, hypoxemia/acidemia, fetal hyperinsulinemia, and impaired cardiac function.

According to the 4th National Obstetrics Registry (NOR), mother with Diabetes in pregnancy had a stillbirth rate of 7.12 per 1000 live births in 2013, 6.53 per 1000 livebirths in 2014 and 6.38 in 2015 [4].

2.4.3 History of Previous Intrauterine Death

According to the National Obstetrics Report ,from 2013 until 2015 43-49% of mothers with stillbirth had previous history of stillbirth [4]. A study published in 2007 was performed in the USA from 1978-1997 using the Missouri maternally linked cohort data. This study aimed to investigate the influence of the history of IUD and the occurrence of a subsequent IUD. Of 404 180 women with information on the first and second pregnancy, 1979 (0.5%) had an IUD in the 1st pregnancy and 402201 (99.5%) did not. Of the 1929 cases of IUD in the 2nd pregnancy,

the risk of IUD was significantly higher in women with history of IUD (22.7 per 1000) as compared to women without a prior stillbirth (4.7 per 1000) . The study concluded that overall, women who had the previous IUD were about five times more likely to experience IUD in the subsequent pregnancy [17].

3.0 JUSTIFICATION OF STUDY

According to to the WHO statistics (2015) , despite marked improvements in antenatal care, more than 2.6 million IUD occur annually according. Sadly, intrauterine deaths are largely invisible in global health indicators, policies, and programs.

Intra-uterine deaths are one of the most stressful events in life . Preventive measures should be taken so that no mother suffers a tragedy.   Furthermore, rates of IUD are a sensitive measure of the quality of intrapartum care.

There is less data available regarding recent studies on IUD in Malaysia, furthermore in the east coast region. This study identifies causes and associated risk factors that results in IUD in Hospital USM as the records regarding intra-uterine deaths in Kelantan are recorded only in Hospital Raja Perempuan Zainab II in 2013-2015 in the National Obstetric Registry [4].

Intrauterine fetal death remains one of the areas in obstetrics in which improvements can be made. This retrospective study gives insight into the local scene of access to medical and obstetric care, treatment of infections, and screening of congenital abnormalities.

4.0 OBJECTIVES

4.1 GENERAL OBJECTIVE

To retrospectively review the intrauterine death in Hospital Universiti Sains Malaysia from 1st of January 2013 until 31st of December 2017.

4.2 SPECIFIC OBJECTIVES

> 4.2.1 To determine the causes of intrauterine death in Hospital Universiti Sains Malaysia.

> 4.2.2 To determine the associated risk factors of intrauterine death in Hospital Universiti Sains Malaysia.

5.0 METHODOLOGY

5.1 STUDY DESIGN, SETTING, AND DURATION

This is a retrospective study to review the intrauterine deaths which were managed in Hospital Universiti Sains Malaysia. This study was conducted using data from January 2013 until December 2017.

The performa form will be divided into 3 sections. The first section will be for patient's details. It will begin with the serial number, age, parity, body mass index (Asian categorization) , education level , presence of antenatal booking and history of smoking. Section 2 will be for the causes of IUD, will be divided into congenital abnormalities, trauma, placental abruption and TORCHES screening. Section 3 will be regarding presence of risk factors such as hypertensive disease, pregestational or gestational diabetes, presence of other medical illnesses and presence of history of IUD.

5.2 REFERENCE AND SOURCE POPULATION

REFERENCE POPULATION : All patients with IUD occurring after 22 weeks of amenorrhea & gestation in Kelantan .

SOURCE POPULATION : All patients with with IUD occurring after 22 weeks of amenorrhea and gestation in Hospital USM from January 2013 until December 2017.

5.3 SAMPLE SIZE CALCULATIONS

The sample size calculation for the first objective using was shown in Table 3.1. The sample size was calculated by using Sample Size Calculator by Wan Nor Arifin. The sample size was determined from the available literature on hypertension and diabetes mellitus (Hossain *et al*., 2009). The parameters required for the determination of the sample size was shown below:

Table 3.1: Sample size calculation for the first objective

Causes of intra-uterine deaths	Proportion (p)	Precision (Δ)	Significance level (α)	Drop-out	Sample size (n)	Corrected sample size after applied drop-out
Placenta abruption	0.0989	0.05	0.05	20%	137	174
Congenital abnormalities	0.0600	0.05	0.05	20%	87	109

The sample size calculation for the second objective using was shown in Table 3.2. The sample size was calculated by using Sample Size Calculator by Wan Nor Arifin. The sample size was determined from the available literature on hypertension and diabetes mellitus (Gardosi *et al*., 2013). The parameters required for the determination of the sample size was shown below:

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Table 3.2: Sample size calculation for the second objective

Risk factors of intra-uterine deaths	Proportion (p)	Precision (Δ)	Significance level (α)	Drop-out	Sample size (n)	Corrected sample size after applied drop-out
Hypertension	0.0380	0.05	0.05	20%	60	75
Diabetes mellitus	0.0290	0.05	0.05	20%	45	57

Based on both sample size calculations for objective 1 and 2, the final sample size selected for the study was 174 patients.

5.4 ETHICS

5.4.1 Declaration of the absence of conflict of interest

I, Dr. Aashreena Inderjit Kaur (MMC 55230) declare an absence of conflict of interest

In my professional judgments or actions on the conduct of the study procedure or the

future interpretation and reporting of the study findings.

5.4.2 Privacy and Confidentiality

The medical records are strictly confidential. Subjects' information was kept on a

password-protected database and was linked only with a study identification number

for this research. The identification number instead of patient identifiers were used on

subject datasheets. All data were entered into a computer that is password protected.

5.4.3 Ethical Board Review and Approval

JEPeM has approved this study (Code: USM/JEpEM/18110753)

5.5 INCLUSION AND EXCLUSION CRITERIA

5.5.1   INCLUSION CRITERIA

- patients diagnosed intra-uterine deaths above 22 weeks of gestation based on period of amenorrhea and gestation from 1st of January 2013 till 31st of December 2017.

- patients who seek treatment in Obstetrics & Gynaecology Department from 1st of January 2013 till 31st of December 2017

- all mode of deliveries

5.5.2   EXCLUSION CRITERIA

- Uncertainty of gestational age (for data which patients are unsure of their last menstrual cycle or irregular menses with no early scan).

- Documents which have missing/incomplete data of 20% or more will be excluded.

5.6 SAMPLING METHOD

The data has been derived from a retrospective case review of intrauterine deaths above 22 weeks period of amenorrhea or gestation in HUSM from the year 2013-2017.

A computer-generated list was obtained from the medical record office. The cases are identified according to the codes of the International Classification of Diseases-Tenth revision (ICD-10).

Keywords used when retrieving records include stillbirth, intrauterine deaths, and fetal demise.