

**A RETROSPECTIVE STUDY OF
MISCARRIAGES AT HOSPITAL USM
FROM JANUARY 2011-DECEMBER 2015**

BY:

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**Dissertation Submitted In Partial Fulfilment Of The
Requirements For The Degree Of Master Of Medicine**

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A RETROSPECTIVE STUDY OF MISCARRIAGES AT HOSPITAL USM FROM JANUARY
2011 TILL DECEMBER 2015

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Introduction: Miscarriage is a common early pregnancy complication. Until now there are still no local data regarding sociodemographic and clinical characteristics of miscarriages. This study addressed these issues by looking into five years of miscarriage cases at Hospital Universiti Sains Malaysia.

Objectives: The aims of this study were to determine proportion of miscarriage and factors associated with miscarriage among Malay in Hospital USM from January 2011 till December 2015, and investigate the sociodemographic and clinical characteristics among study samples.

Methodology: 230 cases that fulfil the criteria were selected randomly from all 736 cases of miscarriage treated at HUSM from the year 2011 – 2015, and all important data such as demography,

reproductive profile, diagnosis or type of miscarriage, presenting symptoms, outcome were taken for analysis.

Results: The proportion of miscarriage in the year 2011 – 2015 ranged between 1.01-2.07%. The commonest type was incomplete miscarriage, followed by missed miscarriage, complete, threatened and inevitable miscarriage. Regardless of the type of miscarriage, vaginal bleeding was the most frequent presenting symptoms. Most of the cases were first-trimester miscarriages which frequently presented with incomplete miscarriage while second-trimester miscarriage presented mostly with missed miscarriage. There was no significant difference between first and second trimester miscarriages in term of age, BMI, marital status, occupational status, parity and history of miscarriage. Only 26 patients had complication related to miscarriage and most of them complicated with significant bleeding. Factors found to be associated with miscarriage in this study were age group 25-29-year-old, normal BMI, parity 1-3 and without any history of miscarriage.

Conclusion: The proportion of miscarriage in HUSM was low. Further study in multiple centres may gain beneficial. Continuous education regarding preparation for optimum health condition before pregnancy must be promoted.

Dr Ahmad Amir Ismail: Supervisor

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II. ABSTRAK

Latar Belakang: Keguguran merupakan antara komplikasi pada awal kandungan. Sehingga kini, tiada data tempatan mengenai keguguran dari aspek sosiodemografi dan ciri klinikal. Kajian ini bertujuan untuk menyentuh mengenai aspek-aspek tersebut dengan mengkaji kes-kes keguguran di Hospital Universiti Sains Malaysia dalam tempoh 5 tahun.

Metodologi: Sebanyak 230 kes yang memenuhi kriteria telah dipilih secara rawak daripada keseluruhan 736 kes keguguran yang telah menerima rawatan di HUSM sepanjang tahun 2011 hingga 2015. Data-data yang penting seperti maklumat demografi, ciri reproduktif, diagnosis dan jenis keguguran, symptom utama dan hasil keguguran telah diambil untuk dianalisa.

Keputusan: Peratusan keguguran bagi tempoh 2011 hingga 2015 adalah dalam julat 1.01-2.07%. Keguguran yang tidak lengkap adalah jenis keguguran yang paling kerap berlaku. Ia diikuti dengan keguguran jenis 'missed', lengkap, terancam and keguguran yang tidak dapat dielakkan. Tanda utama pada semua jenis keguguran adalah pendarahan melalui vagina. Majoriti kes keguguran adalah berlaku pada trimester pertama dengan jenis keguguran tidak lengkap berbanding keguguran pada trimester kedua. Tiada perbezaan ketara antara trimester dengan umur, BMI, status perkahwinan, status pekerjaan, bilangan anak dan sejarah keguguran lampau. Hanya 26 kes melalui komplikasi keguguran dan kebanyakan dari komplikasi tersebut adalah pendarahan yang signifikan. Faktor-faktor yang berkaitan dengan keguguran berlaku pada kumpulan umur 25-29 tahun, BMI yang normal, bilangan anak 1-3 and tanpa sejarah keguguran.

Konklusi: Peratusan keguguran di HUSM adalah rendah. Kajian seterusnya melingkupi pelbagai pusat kesihatan akan membawa lebih manfaat. Pendidikan kesihatan yang berterusan mengenai persediaan sebelum kehamilan bagi menyediakan tahap kesihatan yang optimum perlu diteruskan.

III. ABSTRACT

Background: Miscarriage is a common early pregnancy complication. Until now there are still no local data regarding sociodemographic and clinical characteristics of miscarriages. This study addressed these issues by looking into five years of miscarriage cases at Hospital Universiti Sains Malaysia.

Methodology: 230 cases that fulfil the criteria were selected randomly from all 736 cases of miscarriage treated at HUSM from the year 2011 – 2015, and all important data such as demography, reproductive profile, diagnosis or type of miscarriage, presenting symptoms, outcome were taken for analysis.

Results: The proportion of miscarriage in the year 2011 – 2015 ranged between 1.01-2.07%. The commonest type was incomplete miscarriage, followed by missed miscarriage, complete, threatened and inevitable miscarriage. Regardless of the type of miscarriage, vaginal bleeding was the most frequent presenting symptoms. Most of the cases were first-trimester miscarriages which frequently presented with incomplete miscarriage while second-trimester miscarriage presented mostly with missed miscarriage. There was no significant difference between first and second trimester miscarriages in term of age, BMI, marital status, occupational status, parity and history of miscarriage. Only 26 patients had complication related to miscarriage and most of them complicated with significant bleeding. Factors found to be associated with miscarriage in this study were age group 25-29-year-old, normal BMI, parity 1-3 and without any history of miscarriage.

Conclusion: The proportion of miscarriage in HUSM was low. Further study in multiple centres may gain beneficial. Continuous education regarding preparation for optimum health condition before pregnancy must be promoted.

IV. ABBREVIATION

BMI	Body mass index
D&C	Dilatation & Curettage
EPAU	Early Pregnancy Assessment Unit
ERPOC	Evacuation of POC
hCG	Human chorionic gonadotrophin
HUSM	Hospital Universiti Sains Malaysia
IPI	Inter-pregnancy interval
POC	Product of conception
UK	United Kingdom
VE	Vaginal examination

V. OPERATIONAL DEFINITION

Assisted conception:

The technology used to achieve pregnancy in procedures such as fertility medication, intrauterine insemination, in vitro fertilisation and surrogacy. It is reproductive technology used primarily for infertility treatments.

Cervical os:

Opening in the centre of the ectocervix

Crown-rump length:

The measurement of the length of human embryos and fetus from the top of the head (crown) to the bottom of the buttocks (rump). It is typically determined from ultrasound imagery and can be used to estimate gestational age.

Curette:

Medical procedures which uses a curette (French, meaning scoop) to remove tissue by scraping or scooping.

Decidua:

The term for the uterine lining (endometrium) during pregnancy, which forms the maternal part of the placenta. It is developed under the influence of progesterone and forms highly characteristic cells.

Embryo:

An unborn offspring in the process of development, in particular, a human offspring during the period from approximately the second to the eighth week after fertilization (after which it is usually termed a fetus)

Fetus:

An unborn offspring of a mammal, in particular an unborn human baby more than eight weeks after conception.

Gestational sac:

The cavity of fluid surrounding the embryo. During early embryogenesis it consists of the extra-embryonic coelom, also called the chorionic cavity. It is the only available structure that can be used to determine if an intrauterine pregnancy exists until the embryo is identified.

Monosomy:

The condition of having a diploid chromosome complement in which one (usually the X) chromosome lacks its homologous partner.

Primiparity:

A woman who has given birth to one child or who is giving birth for the first time.

Product of conception:

The medical term used for the tissue derived from the union of an egg and sperm.

Trimester:

A period of three months, primarily as a division of the duration of pregnancy

Trophoblast:

A layer of tissue on the outside of a mammalian blastula, supplying the embryo with nourishment and later forming the major part of the placenta.

Viability:

Ability to survive or live successfully

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1.0 INTRODUCTION

1.1 INTRODUCTION

1.1.1 Introduction to Obstetrics & Gynaecology Department HUSM

Hospital Universiti Sains Malaysia (HUSM) is located at Kubang Kerian, Kelantan. It is a teaching hospital for the School of Medical Sciences, Universiti Sains Malaysia. It was built in 1976, and the construction was completed in 1984. Besides teachings and research, it also provides adequate medical services for the population. It also serves as the referral centre for the state and the neighbouring state in the East Coast.

Department of Obstetrics and Gynaecology is among pioneer department in HUSM. It contributes to significant bed occupancy rate in the hospital. This unit provides outpatient and inpatient services. The heart of department is its labour ward which consists of 7 delivery room with one bed in each room, two beds are for preeclampsia cases, two beds for premature labour cases whose require close monitoring, one bed for high dependency case. In 2016, there was 7627 delivery in a year. Other than labour ward, there were 2 antenatal wards and 1 postnatal ward for obstetrics part. While for gynaecology, there is 1 gynaecology ward that has 36 beds. The admission number to gynaecology ward in year 2016 was 2635.

Apart from antenatal and general gynaecology clinic for outpatient services, there are few other speciality clinic services available. These include detail scan clinic, combine clinic, multiple pregnancy clinic, molar clinic, menopause clinic, urogynaecology clinic, fertility clinic, postnatal clinic and early pregnancy assessment unit/clinic (EPAU). In EPAU, the cases mostly are referral from district hospital, health

clinic or general practitioner. The non-urgent cases from casualty also will be referred to this unit.

1.1.2 Miscarriage

Miscarriage is defined as the loss of pregnancy before viability period which is from the time of conception until 23 weeks of gestation (UK). If the gestation unknown, fetal birth weight less than 500g is included in the criteria. Failed intrauterine pregnancy by sonography or histological evidence is term as clinical miscarriage. Whereas biochemical loss is pregnancy that is demonstrated by raised urinary or serum hCG but fails before ultrasound or histological evidence of the pregnancy.

Miscarriages are unfortunately most common complication of early pregnancy. About quarter of all women who become pregnant will experience pregnancy loss. Majority of them are early pregnancy, before 12 weeks of gestation. The incidence of clinically recognizable miscarriage in general population studies has been consistently reported as 12-15% (Regan and Rai, 2000).

Miscarriage carries a significant number of presentation to casualty and admissions to the gynaecology ward and the numbers have contributed to the establishment of early pregnancy assessment unit/clinic (EPAU). Majority cases in EPAU are from miscarriage group.

Miscarriage has psychological impact on the patient. It is prominent in primiparity, second trimester and recurrent miscarriage. The happiness was stretched from them when miscarriage has been diagnosed. They are likely to experience many emotions including profound disappointment, fear of the process of miscarriage and about the future, sadness, anger, guilt, feeling of inadequacy, failure and helplessness and sometimes prolonged depression (Swanson *et al.*, 2009). Indirectly it affects the

family and community as well due to women nowadays plays a major role in the society. In another perspective, there are also women who attempted to induce abortion due to whatever reasons. In this type of women, other implications have occurred physically or emotionally. The medical consequences depend on the methods of inducing of abortion. Septic abortion and excessive bleeding are among its sequelae.

Although miscarriage can be diagnosed with asymptomatic patient, most of them present to hospital with symptoms of bleeding. The significant amount of bleeding may require blood consumable from the blood bank. Furthermore, majority of asymptomatic patient opted for intervention rather than conservative management. In HUSM, patients need to be admitted for medical and surgical treatment to make sure the complications that may arise will be under control with the availability of the emergency equipment and blood bank services. For those who require surgical treatment, it will consume operation time and anaesthetic medications.

Normal pregnancy

The process involves from fertilization until viable fetus is complicated. As in general, it begins when a healthy haploid spermatozoon with normal genetic contained fertilize healthy haploid ovum with normal genetic. The second meiotic division of the oocyte is only completed after fertilization. Following fertilization, the ovum moves towards the uterus aided by the muscle activity of the tube and by the cilia. Early development of the fertilized ovum depends on the nutrients derived from the secretion from numerous glandular secretion cells at the medial end of the tube. From fallopian tube, it takes about four days to reach the uterine cavity, which is lined by a spongy secretory endometrium receptive to implantation of the blastocyst. Within 30 hours of

fertilization, the first cell division or cleavage occurs. Within 12 hours, a second cleavage occurs when each of daughter cells divides into two again by mitotic division. It follows by subsequent cleavage. When embryo has between 16 and 32 cells, after the fourth cleavage division, it undergoes a process known as compaction and become morula then fluid-filled cavity develops between the cells and blastocyst is formed. Blastocyst implants into the secretory endometrium of the uterus about six days after fertilization. Trophoblast cells produce a proteolytic enzyme which allows invasion into the endometrium. By the end of 10 days, the early embryo has burrowed into the endometrium, and it is completely covered. It extracts nutrient from endometrial secretions and is already producing human chorionic gonadotrophin (hCG). The trophoblast cells go on to form the placenta. The inner cell mass then divided and formed layers of cells which differentiate into embryonic ectoderm, endoderm and ectoderm. This process followed with organogenesis (Prakash *et al.*, 2006).

Pathogenesis

Spontaneous miscarriage which occurs within the first 12 weeks of gestation constitutes more than 80% of the cases. Death of the embryo or fetus is usually accompanied by adjacent tissue necrosis that stimulates uterine contractions and expulsion. An intact gestational sac is filled with fluid and may or may not contain an embryo or fetus. In determining the cause of early miscarriage is to find the cause of fetal death (Barbara L. Hoffman, 2012). The spontaneous loss in the second trimester is estimated at 1.5 – 3%, and after 16 weeks it is only 1% (Simpson, 2007). Second trimester miscarriages are due to multitude of causes such as fetal anomalies, uterine defects, placental causes and maternal disorders.

Risk factors

Genetic factors are the most frequent cause of early embryonic loss. Chromosomal abnormalities were observed in approximately 20% of in vitro fertilised embryos that are ostensibly normal (El-Mekkawi *et al.*, 2015). It frequently seen in morphologically normal embryos suggested that the frequency would be higher in abnormal morphology; the most likely explanation for morphological abnormalities is genetic factors. Autosomal monosomy proved non-viable. Monosomies usually aborted within 4-5days of conception i.e. around implantation. Trisomies were lost later, with only a few surviving until live birth (Balsells *et al.*, 2016).

In first trimester miscarriage, cytogenetic abnormalities are by far the most frequent explanation for the 12-15% of clinically recognised pregnancy losses (Lachelin, 1985). The frequency of chromosomal aberrations is approximately 50%. Meanwhile, in second-trimester miscarriage, chromosomal abnormalities more similar to those observed in live-born infant: trisomies 13, 18 and 21; monosomy X; chromosomal sex polysomies (Regan *et al.*, 1990).

Several risk factors were identified as contributing factors to miscarriages. In one cohort study, risk of miscarriage was significantly increased in women at higher age; lower body mass index and lower serum progesterone concentrations (≤ 12 ng/ml) before the onset of the miscarriage (Arck *et al.*, 2008). Women with subsequent miscarriage also perceived higher levels of stress/demands (supported by higher concentrations of corticotropin-releasing hormone) and revealed reduced concentrations of progesterone-induced blocking factor. According to RCOG, the risk factors for recurrent miscarriages categorised into antiphospholipid syndrome, genetic factors, anatomical factors, endocrine factors, immune factors and epidemiological factors.

Assessment and diagnosis

The most common signs of miscarriage are vaginal bleeding and abdominal pain in early pregnancy. These problems should always be evaluated by a clinician. However, bleeding and discomfort can occur in normal pregnancies. In many cases, bleeding resolves spontaneously, and the pregnancy usually continues without further problems.

Most of the time, diagnoses of miscarriage is easy to verify with the wide availability of ultrasonography. In normal early pregnancy, two questions must be answers which are confirmatory of intrauterine pregnancy and the viability of the pregnancy. It is important to differentiate between a real intrauterine gestational sac and the pseudogestational sac that result from the decidual response of the uterus to an ectopic pregnancy. Characteristically, the early intrauterine gestational sac is eccentrically located within the uterine cavity and is surrounded by an asymmetrical trophoblast ring. This asymmetry distinguished normal pregnancy from ectopic gestation and hormone-induced changes associated with normal menstrual cycle. At this stage, the normal sac has two layers which represent the decidua capsularis and parietalis. This double echogenic wall appearance is reportedly missing in pseudosac (Abdallah *et al.*, 2011). Sonographic identification of the yolk sac confirms the presence of an intrauterine pregnancy. However, its presence does not guarantee that the intrauterine pregnancy is normal. Identification of cardiac activity is an indication of viable pregnancy. The earliest recorded cardiac activities detected by TVS in one study occurred at 40days from the LMP, at mean gestational sac diameter of 9.3mm, and CRL of 2mm (Rempen 1990). However, these parameters cannot be used consistently to diagnose viability as their identification is operator and equipment dependent. While embryo smaller than 5mm may have visible cardiac activity, one-third of embryos with

CRL less than 5mm did not demonstrate cardiac activity subsequently shown to be normal (Pennel et al. 1990, Levi et al. 1990). Therefore, the diagnosis of early demise should not be made by TVS in embryo measuring less than 5mm without a visible heartbeat. In TAS, provided high-resolution equipment gives images of good technical quality, it should always be possible to see the cardiac action whenever the embryo is visualised.

Management

Expectant, medical and surgical management are all reasonable options provided there is absent of significant bleeding or infection. The definitive treatment is the surgical intervention however it may not be necessary for all women and also carries the risk associated with invasive procedure. Meanwhile, expectant and medical management may obviate curettage, but some of it is associated with unpredictable bleeding and need for emergency procedure under anaesthesia. In one observational study, majority women with first trimester miscarriage end up with spontaneous resolution (Barbara L. Hoffman, 2012).

The principle of treatment during and after a miscarriage is to prevent bleeding and infection. The most common procedure performed to stop bleeding is a dilation and curettage (D&C). Since the cause of most miscarriages is due to chromosomal abnormalities, there is not much that can be done to prevent them. One vital step is to get as healthy as they can before conceiving to provide a healthy atmosphere for conception to occur.

LITERATURE REVIEW

Miscarriage is one of the most frequent problems in human pregnancy. The incidence among clinical pregnancies is about 12-15%, but including early pregnancy losses, it is 17-22% (Garcia, 2002). Until now, there is no universal agreement regarding cut of period that classifies the miscarriage. While UK takes the viability started at 24 weeks gestation, according to WHO, miscarriage was classified up to 20 weeks gestation.

According to a national survey in the United States that analysing perception of miscarriage, they found that most men and women wrongly believe that miscarriage is highly uncommon and many do not understand its causes. Studies show that women and couple who experience miscarriage may pay a high emotional price because there is a lack of knowledge about how common miscarriage is and its causes. About 40% of the women who had a miscarriage believed they had done something wrong to cause it and felt guilty (Swanson et al., 2009; Thapar and Thapar, 1992). Charles and Kimberly coated that a miscarriage is a significant painfully devastating emotional loss for the couple and need to be treated as such. As miscarriage cause psychology disturbance to the couple, that can further affect the future pregnancy. Baseline depressive symptom will influence subsequent miscarriage (Sugiura-Ogasawara et al., 2002). The counselling and explanation to the patient and family is an important aspect of managing this group of problem.

One study conducted in China which was a Hospital based matched case-control study. They looked for the risk factors for first trimester miscarriage and found that factors that independently associated with increased risk are history of miscarriage, repeated induced abortion, working night shift and frequent staying up late. Meanwhile, vitamin

supplement and regular physical activity reduced the risk of miscarriage. While a study conducted at UK population-based, case-control study was done to look for association between biological, behavioural and lifestyle risk factor, and risk of miscarriage. They found that increasing maternal age, previous miscarriage, assisted conception, low pre-pregnancy BMI, alcohol, feeling stress and high paternal age are associated with higher risk of miscarriage. Whereas history of previous life birth, nausea, vitamin supplement and eating fresh fruit and vegetables are associated with reduced risk of miscarriage.

It is well known that miscarriage's risk increases with maternal age. Elise investigated both maternal and paternal age effect on miscarriage risk. She found that the risk of miscarriage was higher if the woman was aged > 35 years and man was aged > 40years (de La Rochebrochard and Thonneau, 2002).

Obesity is a major issue that has proven to cause significant medical problems. Unfortunately, Malaysia's obesity rate is the top ranking in Asia. Almost half of Malaysians are obese or overweight. A report in 2016 showed 18% or more than 5 million people were classified under obese category. A further 30% are overweight. Several studies look for association of miscarriage with body weight. Some claim that underweight associated with higher risk of miscarriage (Arck et al., 2008; Balsells et al., 2016). However, more superior study (meta-analysis) shown vice versa (Metwally et al., 2008).

The Leiden mutation is a discovery. It is the primary cause of inherited thrombophilia and has been found in 20-60% of deep vein thrombosis (DVT) cases. The risk of having

at least one miscarriage or infertility problems was 1.5 times greater for Leiden mutation carrier than control (Bare et al., 2000).

Another significant cause contributing to miscarriage is an assisted reproductive technology. The rate of clinical pregnancy loss in ART was around 18.2% (Souter et al., 2014). During in vitro fertilization-embryo transfer cycles (IVF-ET) many morphologically normal embryos fail to implant. One explanation for implantation failure is the existence of chromosomal aneuploidy or single gene defects. During IVF many good quality embryos are chromosomally abnormal. In older women, women with a history of pregnancies with aneuploid fetuses or multiple IVF failures, PGD may lead to an increased rate of implantation, and significantly reduce the risk of chromosomally unbalanced offspring and pregnancy loss. Expanding the indications for transferring only euploid embryos might lessen the need for repeated cycles of ovarian stimulation and egg retrieval, and improve pregnancy rates for all patients undergoing IVF (Souter et al., 2014).

1.2 RATIONALE FOR THE STUDY

This study is important in looking for the risk factors of miscarriage among Malays at HUSM. According to Department of Statistics in 2015, from total of 1 718 200 people in Kelantan, 92.3% were among Malays. There were so far no local data regarding the proportion, socio-demographic and clinical characteristics of miscarriage. This study therefore was planned to address these issues. Other than counselling purposes, it provides data that can be compared to in future research. It is also may stimulate others to do study especially on biochemical ground that predispose to miscarriage. Finally it will help clinician to recognize pregnant women at risk who may require extra monitoring and also who might benefit from therapeutic interventions especially during the first week of pregnancy in attempt to prevent or reduce the incidence of miscarriage.

1.3 GENERAL AND SPECIFIC OBJECTIVES

1.3.1 General objective:

1.3.1.1 To study regarding miscarriage cases among Malays at HUSM from
January 2011 till December 2015

1.3.2 Specific objectives

1.3.2.1 To determine the proportion of miscarriage among Malay in HUSM
from January 2011 till December 2015

1.3.2.2 To describe socio-demographic and clinical characteristics among
study samples

2.0 STUDY PROTOCOL

2.1 DOCUMENTS SUBMITTED FOR ETHICAL APPROVAL

2.1.1 Study Proposal

TITLE PAGE (PROPOSAL)

**Department of Obstetrics and Gynaecology,
School of medical sciences,
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Kelantan, Malaysia**

Dissertation Proposal

**Partial fulfilment of Master of Medicine (Obstetrics and Gynaecology)
University Sains Malaysia**

Research Topic:

**A Retrospective Study of Factor Associated With Miscarriage in Hospital USM
from January 2011 – December 2015**

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1. INTRODUCTION

Miscarriage is defined as the spontaneous loss of pregnancy before viability period which are from the time of conception until 23 weeks of gestation (UK). If the gestation unknown, fetal birth weight less than 500g is included in the criteria. Miscarriages are unfortunately most common complication of early pregnancy. About quarter of all women who become pregnant will experience pregnancy loss. Majority of them are early pregnancy, before 12 weeks of gestation. The incidence of clinically recognizable miscarriage in general population studies has been consistently reported as 12-15%.

The most common signs of miscarriage are vaginal bleeding and abdominal pain in early pregnancy. These problems should always be evaluated by a clinician. However, bleeding and discomfort can occur in normal pregnancies. In many cases, bleeding resolves spontaneously and the pregnancy continues normally without further problems.

There are many types of miscarriage based on clinical classification:

a) **Threatened miscarriage:**

Bloody vaginal discharge or bleeding appears through a closed cervical os during the first half of pregnancy.

b) **Missed miscarriage:**

Failure of pregnancy is identified before expulsion of the product of conception (Isabel Stabile, 1992). Dead products of conception were retained for a period of time in the uterus with a closed cervical os

c) **Inevitable miscarriage:**

Characterised by vaginal bleeding, cramping lower abdominal pain associated with an open cervical os

d) **Incomplete miscarriage:**

Internal os opens and allows passage of blood. The fetus and placenta may partially extrude through the open os.

e) **Complete miscarriage:**

Characterised by lower abdominal cramping and passage of products followed with absence of pain and bleeding or minimal bleeding if present. The cervical os is closed.

f) **Induced abortion:**

Deliberate termination of pregnancy before viability of fetus

g) **Septic abortion:**

Infection either ascending from the lower genital tract or iatrogenically introduced while performing induced abortion. It can manifest as local genital tract infection or in severe cases as a sepsis.

h) **Recurrent miscarriage:**

Three or more consecutive pregnancy losses at 20 weeks's gestation or less or with fetal weights less than 500g.

Genetic factors are the commonest cause of early embryonic loss. Chromosomal abnormalities were observed in approximately 20% of in vitro fertilised embryos that are ostensibly normal. It seen frequently in morphologically normal embryos suggested that the frequency would be higher in abnormal morphology ie most likely explanation for morphological abnormalities is genetic factors. Autosomal monosomy proved non-viable. Monosomies usually aborted within 4-5days of conception (ie around implantation). Trisomies were lost later, with only a few surviving until live birth.

In first trimester miscarriage, cytogenetic abnormalities are by far the most frequent explanation for the 12-15% of clinical recognised pregnancy losses. The frequency of chromosomal abnormalities is approximately 50%. Meanwhile, in second trimester miscarriage, chromosomal abnormalities more similar to those observed in live-born infant: trisomies 13, 18 and 21; monosomy X; sex chromosomal polysomies.

Several risk factors were identified as contributing factors to miscarriages. In one cohort study, risk of miscarriage was significantly increased in women at higher age; lower body mass index and lower serum progesterone concentrations (≤ 12 ng/ml) prior to the onset of the miscarriage (Arck *et al.*, 2008). Women with subsequent miscarriage also perceived higher levels of stress/demands (supported by higher concentrations of corticotrophin-releasing hormone) and revealed reduced concentrations of progesterone-induced blocking factor. According to RCOG, the risk factors for recurrent miscarriages categorised into antiphospholipid syndrome, genetic factors, anatomical factors, endocrine factors, immune factors and epidemiological factors.

Most of the time, diagnoses of miscarriage is easy to verify with the wide availability of ultrasonography. In normal early pregnancy, 2 questions must be answers which are confirmatory of intrauterine pregnancy and the viability of the pregnancy. It is important to differentiate between a true intrauterine gestational sac and the pseudogestational sac that result from the decidual response of the uterus to an ectopic pregnancy. Characteristically, the early intrauterine gestational sac is eccentrically located within the uterine cavity and is surrounded by an asymmetrical trophoblast ring. This asymmetry distinguished normal pregnancy from ectopic gestation and from hormone-induced changes associated with normal menstrual cycle. At this stage the normal sac has two layers which represent the decidua capsularis and parietalis. This double echogenic wall appearance is reportedly missing in pseudosac. Sonographic identification of the yolk sac confirms the presence of an intrauterine pregnancy. However, its presence does not guarantee that the intrauterine pregnancy is normal. Identification of cardiac activity is an indication of viable pregnancy. The earliest recorded cardiac activities detected by TVS in one study occurred at 40days from the LMP, at mean gestational sac diameter of 9.3mm, and CRL of 2mm (Rempen 1990). However, these parameters cannot be used consistently to diagnose viability as their identification is operator and equipment dependent. While embryo smaller than 5mm may have visible cardiac activity, one-third of embryos with CRL less than 5mm did not demonstrate cardiac activity subsequently shown to be normal (Pennel et al 1990, Levi et al 1990). Therefore, the diagnosis of embryonic demise should not be made by TVS in embryo measuring less than 5mm without a visible heart beat. In TAS, provided high resolution equipment gives images of good technical quality, it should always be possible to see the cardiac action whenever the embryo is visualised.

Expectant, medical and surgical management are all reasonable options provided there is absent of serious bleeding or infection. The definitive treatment is by the surgical intervention however it may not necessary for all women and also carries the risk associated with invasive procedure. Meanwhile, expectant and medical management may obviate curettage, but some of it is associated with unpredictable bleeding and need for emergency procedure under anaesthesia. In one observational study, majority women with first trimester miscarriage end up with spontaneous resolution.

The principle of treatment during and after a miscarriage is to prevent haemorrhage and/or infection. The most common procedure performed to stop bleeding is a dilation and curettage (D&C). Since the cause of most miscarriages is due to chromosomal abnormalities, there is not much that can be done to prevent them. One vital step is to get as healthy as they can before conceiving to provide a healthy atmosphere for conception to occur.

This study will explore the factors associated with miscarriage among Malays women in HUSM. All spontaneous miscarriages will included in the study stunning first, second and recurrent miscarriages. However threatened miscarriage will not include in this study.

2. PROBLEM STATEMENT AND STUDY RATIONALE

Miscarriage carries a significant number of presentation to casualty and admissions to the gynaecology ward and the numbers have contribute to the establishment of early pregnancy assessment unit / clinic (EPAU). Although EPAU has other cases for assessment, the majority of it is in miscarriage group.

Miscarriage has psychological impact to the patient. It is more prominent in primiparity, second trimester and in recurrent miscarriage. The happiness was stretched from them once miscarriage was diagnosed. They are likely to experience a number of emotions including profound disappointment, fear of the process of miscarriage and about the future, sadness, anger, guilt, feeling of inadequacy, failure and helplessness and sometime prolonged depression. Indirectly it affects the family and community as well due to women nowadays plays a major role in the society. In other perspective, there are also women who attempted to induce abortion due to whatever reasons. In this type of women, other implications have occurred physically or emotionally. The medical implications depend on the methods of inducing of abortion. Septic abortion and excessive bleeding are among its sequelae.

Although miscarriage can be diagnosed with asymptomatic patient, most of them present to hospital with a symptoms of bleeding. The significant amount of bleeding may require blood consumable from the blood bank. Furthermore, majority of asymptomatic patient opted for intervention rather than conservative management. In HUSM, patients need to be admitted for medical and surgical treatment to make sure the complications that may arise will be under controlled with the availability

of the emergency equipment and blood bank services. For those who require surgical treatment, it will consume operation time and anaesthetic medications.

This study is important to look for the risk factors of miscarriage among Malays in HUSM. According to Department of Statistics in 2015, from total of 1 718 200 people in Kelantan, 92.3% are among Malays. As up to time of this paper are writing, there are no local data regarding the incidence and factors associated with miscarriage. This study will produce local statistical data for that period of time. Other than counselling purpose, it provide data that can be compare in future. It is also stimulate others to do study especially in biochemical ground that associated with miscarriage. Finally it will help clinician to recognize pregnant women who require extra monitoring and also who might benefit from therapeutic interventions especially during the first week of pregnancy in attempt to prevent or reduce the incidence of miscarriage.

3. **LITERATURE REVIEW**

Miscarriage is one of the most frequent problems in human pregnancy. The incidence among clinical pregnancies is about 12-15% but including early pregnancy losses it is 17-22% (Garcia, 2002). Until now, there is no universal agreement regarding cut of period that classify the miscarriage. According to WHO, miscarriage was classify up to 20w gestation. While UK take the viability started at 24 weeks gestation.

According to a national survey in US that analysing perception of miscarriage, they found that most men and women wrongly believe that miscarriage is highly uncommon and many do not understand its causes. Studies shows that women and couple who experience miscarriage may pay a high emotional price because there is a lack of knowledge about how common miscarriage is and its causes. About 40% of the women who had a miscarriage believed they had done something wrong to cause it and felt guilty (Swanson *et al.*, 2009; Thapar and Thapar, 1992). Charles and Kimberly coated that a miscarriage is a significant painfully devastating emotional loss for the couple and need to be treated as such. As miscarriage cause psychology disturbance to the couple, that can further affect the future pregnancy. Baseline depressive symptom will influenced subsequent miscarriage (Sugiura-Ogasawara *et al.*, 2002). The counselling and explanation to the patient and family is an important aspect in managing this group of problem.

One study conducted at China which was a Hospital based matched case control study. They looked for the risk factors for first trimester miscarriage and found that factors that independently associated with increased risk are history of miscarriage, repeated induced abortion, working night shift and frequent staying up late. Meanwhile, vitamin supplement and regular physical activity reduced the risk of miscarriage. While a study conducted at UK; population based, case control study was done to look for association between biological, behavioural and life style risk factor, and risk of miscarriage. They found that increase maternal age, previous miscarriage, assisted conception, low pre pregnancy BMI, alcohol, feeling stress and high paternal age are associated with higher risk of miscarriage. Whereas history of

previous life birth, nausea, vitamin supplement and eating fresh fruit and vegetables are associated with reduced risk of miscarriage.

It is well known that miscarriage risk increase with maternal age. Elise investigated both maternal and paternal age effect on miscarriage risk. She found that the risk of miscarriage was higher if the woman was aged ≥ 35 years and man was aged ≥ 40 years (de La Rochebrochard and Thonneau, 2002).

Obesity is a major issue that has proven to cause significant medical problems. Unfortunately, Malaysia's obesity rate is the top ranking in Asia. Almost half of Malaysians are obese or overweight. Report in 2016 showed 18% or more than 5 million people were classified under obese category. A further 30% are overweight. There were several studies that look for association of miscarriage with body weight. Some claim that underweight associated with higher risk of miscarriage (Arck *et al.*, 2008; Balsells *et al.*, 2016). However more superior study (meta-analysis) shown vice versa (Metwally *et al.*, 2008).

The Leiden mutation is a new discovery. It is the main cause of inherited thrombophilia and has been found in 20-60% of deep vein thrombosis (DVT) cases. The risk of having at least 1 miscarriage or infertility problems was 1.5 times greater for Leiden mutation carrier then control (Bare *et al.*, 2000).

Other significant cause contributing to miscarriage is an assisted reproductive technology. The rate of clinical pregnancy loss in ART is around 18.2% (Souter et al, 2014). During in vitro fertilization-embryo transfer cycles (IVF-ET) many morphologically normal embryos fail to implant. One explanation for implantation failure is the existence of chromosomal aneuploidy, or single gene defects. During IVP many good quality embryos are chromosomally abnormal. In older women, women with a history of pregnancies with aneuploid fetuses or multiple IVF failures, PGD may lead to an increased rate of implantation, and significantly reduce the risk of chromosomally unbalanced offspring and pregnancy loss. Expanding the indications for transferring only euploid embryos might reduce the need for repeated cycles of ovarian stimulation and egg retrieval, and improve pregnancy rates for all patients undergoing IVF (Souter et al, 2014).

4. **TARGET RESEARCH QUESTIONS**

- 1) What is the proportion of miscarriage
- 2) How is the distributions of the type of miscarriages
- 3) What are the factors associated with miscarriages

5. OBJECTIVE

- a) General objective: To study regarding factor associated with miscarriage among Malays in HUSM from year 2011 till 2015
- b) Specific objectives
 - 1) To determine the proportion of miscarriage among Malay in HUSM from January 2011 till December 2015
 - 2) To describe sociodemographic and clinical characteristics among study samples
 - 3) To determine factors associated with miscarriage among Malays in HUSM.

6. RESEARCH DESIGN

Retrospective study

7. STUDY AREA

Hospital USM is a university tertiary hospital located at Kubang Kerian, Kelantan. It is a referral hospital in where it be referred by few district hospital and health clinic. The Obstetrics and Gynaecology Department is an important department as it contribute to significant percentage of patient's admission to the wards and attendance to specialist clinic. The total numbers of delivery is a range of 7000 per year.