A PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS THE EFFICACY OF ORAL PROGESTOGEN IN PATIENTS WITH FIRST TRIMESTER THREATENED MISCARRIAGE

BY

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ABSTRACT

Miscarriage is a common complication of pregnancy occurring in 15-20% of all clinically recognized pregnancies. Threatened miscarriage is characterised by vaginal bleeding associated with or without abdominal pain, where the cervix is closed and the fetus is still viable intrauterine. The aim of this study was to establish the efficacy of oral progestogen (intervention group) compared to conservative management, which was bed rest (control group) in subjects with the first trimester threatened miscarriage. The primary outcome of this study was represented based on the number of miscarriages by 20 weeks of gestation. This prospective observational study was conducted at gynaecology ward and Early Pregnancy Assessment Unit (EPAU) of Hospital Sultanah Nur Zahirah and the Department of Obstetrics and Gynaecology, Sultan Ahmad Shah Medical Centre IIUM for ten months, from June 2019 until March 2020. A total of 217 pregnant women were recruited as the subjects in this study. They were presented with threatened miscarriage of less or equal to 12 weeks of gestation, who fulfilled inclusion criteria and provided informed consent. They were divided into the intervention and control groups. In the intervention group, the subjects were given 40 mg (4 tablets) of dydrogesterone orally at once, then 10 mg (1 tablet) in the interval of every 8 h until the symptoms abate, while the subjects in the control group were advised for bed rest as conservative management. The baseline demographic data in both studied groups were similar and there was no significant (p>0.05) difference in age, BMI, parity, and time interval to pregnancy in both groups. Based on the outcome, there was a smaller number of miscarriages in the intervention group (23, 46%) compared to the control group (27, 54%). However, it was not statistically significant (p>0.05). In conclusion, oral progestogen therapy was an ineffective way to reduce the number of miscarriages in patients with the first trimester threatened miscarriage.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion; it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of Obstetrics and Gynaecology.

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DECLARATION

I hereby declare that this dissertation is the result of my own investigation, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Mazrin Nur Mohd Ali

Signature…… Date ….....

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Signature Date

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LIST OF ABBREVIATIONS

HSNZ	Hospital Sultanah Nur Zahirah
O&G	Obstetrics & Gynaecology
SASMEC	Sultan Ahmad Shah Medical Centre
IIUM	International Islamic University of Malaysia
EPAU	Early pregnancy assessment unit
PAC	Patients Assessment Centre
BP	Blood pressure
MCC	Maternity & Child Centre
CRF	Case report form
e.g.	*(exempli gratia)* : for example
etc.	*(et cetera)*: and so forth
et al.	*(et alia)*: and others
vs.	*(versus)* : against
g	gramme
cm	centimetre
nmol/L	Nanomoles per litre
kg	kilogramme
kg/m^2	Kilogramme per meter square
IVIg	Intravenous Immunoglobulin
HCG	Human Chorionic Gonadotropin
MeSH	Medical Subject Headings
PIBF	Progesterone-induced blocking factor
SAE	Serious adverse event
EDD	Estimated due date
REDD	Revised estimated due date
LMP	Last menstrual period
BMI	Body mass index
IUGS	intrauterine gestational sac
n	Number
PCOS	Polycystic Ovarian Syndrome
pctl	percentile
RCOG	Royal College of Obstetricians and Gynaecologists
SD	Standard deviation
TVS	Transvaginal scan
WHO	World Health Organization
TCM	Traditional Complementary Medicine
SD	Standard deviation
RR	relative risk
CI	Confidence interval
IPI	Interpregnancy interval

CHAPTER ONE

INTRODUCTION

1.1 RESEARCH BACKGROUND

Miscarriage is a spontaneous pregnancy loss that occurs before the foetus reaches viability around 20-24 weeks of gestation from the last menstrual period. If the gestation is unknown, it refers to the loss of the embryo or foetus with a birth weight of less than 400-500 g (RCOG, 2011; Schindler et al., 2015) Miscarriage is a common complication of pregnancy occurring in 15-20% of all clinically recognized pregnancies(Schindler et al., 2015).

Threatened miscarriage is defined as bleeding during the first 20 weeks of gestation and cervical opening remains closed (Chan et al., 2020). The condition has an impact on the individual emotional wellbeing due to the uncertainty of the pregnancy outcome(Zhu et al., 2018,Boryri et al., 2020). It is also reported that women with threatened miscarriage have a higher chance to get preterm delivery, intrauterine growth restriction, antepartum haemorrhage, and prelabour rupture of membrane as compared to women without threatened miscarriage (Ozdemirci et al., 2014). Some of the risk factors that have been studied include work and lifestyle environment, maternal age, endocrine, history of miscarriage, paternal age, and more as listed in Table 1.1 (Li et al., 2017).

Table 1.1 Risk factors for miscarriage
Source: Adopted from Li et al. (2017)

Characteristics	**Risk factors**
Maternal characteristics and background history	Maternal age > 35 years old or paternal age > 45 years old.
	Previous miscarriage(s)
	Poorly controlled metabolic and endocrine diseases.
	Caffeine intake
	Active drug user
	Low BMI
	Behavioural factors and occupational exposure
Ultrasound features	Discrepancy between gestational age and crown rump length
	Discrepancy between menstrual and sonographic age of > 1 week
	No fetal heart activity
	Fetal bradycardia < 120/min
	Empty gestational sac > 15-17 mm diameter without yolk sac
	Gestational sac > 13 mm diameter without yolk sac
	Subchorionic hematoma

Progesterone is an important hormone in pregnancy, which is secreted by granulosa cells of the ovary. It provides early pregnancy support until placental production takes over at 10 to 12 weeks of gestation (Czyzyk et al.,2017). A low level of circulating progesterone has been associated with threatened miscarriage (Ku et al.,

2018). Some of the roles of progesterone in early pregnancy are preventing embryo rejection from the mother, promoting uterine quiescence, and preventing uterine contractions (Czyzyk et al.,2017). Therefore, the lack of progesterone could be the cause of miscarriage. Ku et al. (2018) conducted a study to evaluate distribution of serum progesterone in normal pregnancies versus pregnancies complicated with threatened miscarriage. As shown in Figure 1.1, the study reported that the serum progesterone varied according to gestational age and the mean was significantly higher in the normal pregnancy, which was categorised as a low-risk group compared to those who threatened miscarriage which categorised as a high-risk group.

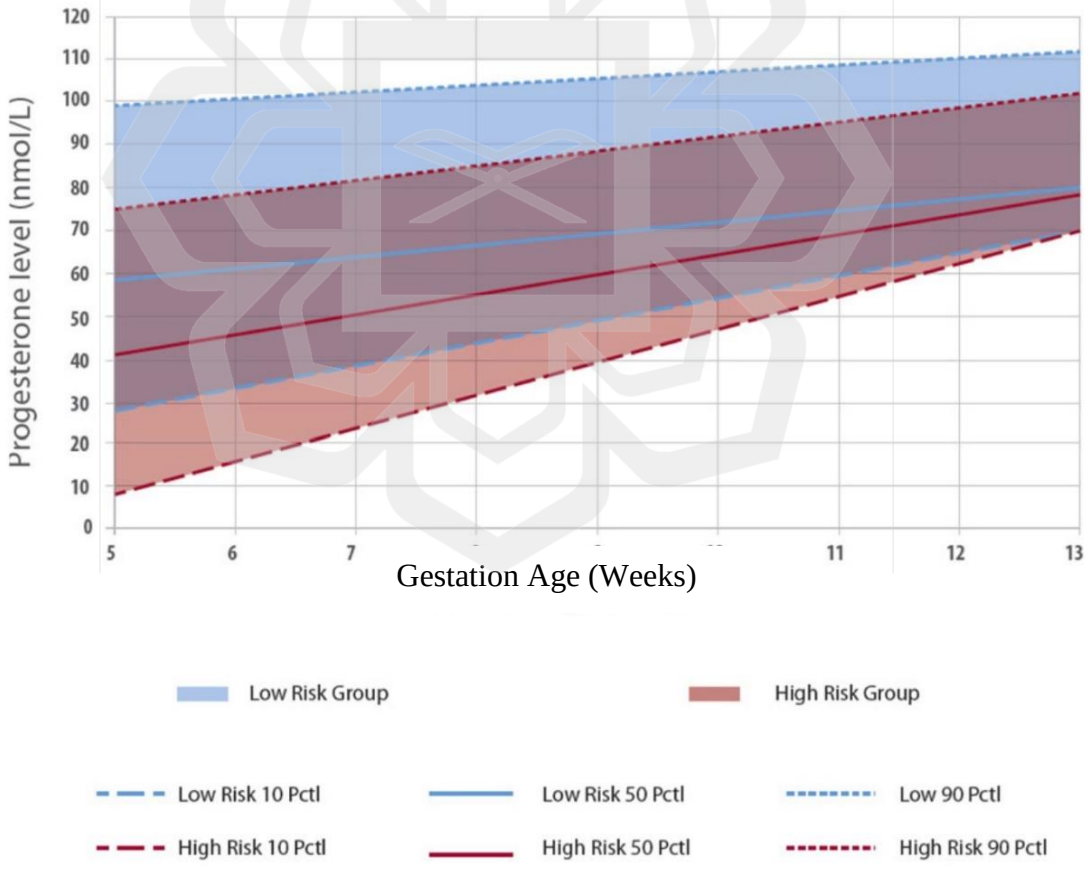

Figure 1.1 Distribution of serum progesterone across gestation weeks 5-13 amongst women with normal pregnancy (Low Risk Group) vs. threatened miscarriage (High Risk Group)
Source: Adopted from Ku et al.(2018)

Various effective treatment modalities for threatened miscarriage have been reported such as bed rest and expectant management (wait and see policy), progesterone and HCG, as well as uterine muscle relaxant drug (Li et al., 2017). Bed rest is one of the acceptable and mostly used treatments for threatened miscarriage with or without subchorionic hematoma. The prognostic outcome following this treatment has shown a promising result (Li et al., 2017). Since 1950's progestogens have been prescribed for miscarriage prophylaxis. It is available commercially and has been revised for its pharmacokinetics and pharmacodynamics. Routes of administration may influence the efficacy of progesterone therapy in early pregnancy, which include oral, intramuscular, and vaginal. Oral administration offers optimal compliance, and the optimal dose is between 100 and 200 mg/day depending on the patient's body weight. Some of the disadvantages for oral administration of progestogens are the extreme variability in the plasma concentrations because of the variety of gastric filling and enterohepatic cycle.

Dydrogesterone is an example of oral progestogen that has been used for many years for the treatment of threatened miscarriage. The recent meta-analysis by Wahabi et al. (2018) concluded that oral dydrogesterone has a significant reduction in the incidence of miscarriage in patients with threatened miscarriage. In Malaysia, there were two reported randomized controlled trials conducted by Pandian (2009) and Omar et al. (2005) with 191 and 154 subjects, respectively which revealed the beneficial effect of dydrogesterone on maintaining pregnancy in women with threatened miscarriage. However, both studies were performed almost 10 years ago with small sample size. Thus, the purpose of this study is to evaluate the effectiveness of oral progestogen in the first trimester threatened miscarriage, particularly in low-risk patients (without a history of recurrent miscarriage and luteal support) as well as to get the local and recent data for treatment of threatened miscarriage.

1.2 PROBLEM STATEMENT

Dydrogesterone has been used for many years for the treatment of first trimester threatened miscarriage. However, it is not routinely used in the local setting referring to Hospital Sultanah Nur Zahirah (HSNZ) and Sultan Ahmad Shah Medical Centre (SASMEC), Kuantan, Pahang. Hence, this study was designed as a prospective cohort study to explore the efficacy of oral progestogen for treating the first trimester threatened miscarriage among patients in these two hospitals. It involved a larger sample size compared to previous studies (Omar et al., 2005; Pandian, 2009) to collect recent data regarding treatment with dydrogesterone as well as to convince the doctors to use dydrogesterone as the treatment of threatened miscarriage.

1.3 RESEARCH OBJECTIVES

1.3.1 General objectives

To determine the effectiveness of oral progestogen in patients with the first trimester threatened miscarriage.

1.3.2 Specific objectives

1. To compare the number of patients having miscarriage after progestogen therapy and conservative management.
2. To determine ongoing pregnancy by 20 weeks of gestations after receiving oral progestogen therapy and in conservative group.

1.4 RESEARCH HYPOTHESIS

Progestogen therapy significantly reduce the number of miscarriages in women with the first trimester threatened miscarriage.

CHAPTER TWO

LITERATURE REVIEW

2.1 PROGESTOGEN COMPOSITION, PHYSIOLOGICAL AND SIDE EFFECTS.

Progesterone is an important steroid hormone in pregnancy (Czyzyk et al., 2017). It is secreted by granulosa cells of the ovary and works to support the early development of embryo until the embryo is taken over by placenta at about 10 to 12 weeks of pregnancy. Progesterone deficiency has been reported to threaten pregnancy(Ku et al., 2018). However, the roles of progesterone in implantation failure and miscarriage have been continuously revised (Czyzyk et al., 2017). Hence, the therapeutic purpose of progesterone in early pregnancy is used to prevent and treat threatened miscarriage and recurrent miscarriage. In threatened miscarriage, it helps in immunological factors, luteinic and neuroendocrine deficiencies, and myometrial hypercontractility.

Various terms have been used interchangeably between progestogen, progestogen, gestogen, gestagen, and progestin to describe the synthetic agent that binds to the progesterone receptor. It is widely used as hormonal birth control, menopausal hormonal therapy, and fertility and pregnancy support (Micks et al., 2015). The progestogen is a type of medication that produces a similar effect to the natural female sex hormone. Different progestogens have different progestogenic potency, receptor-binding selectivity, bioavailability, and route of administration. Thus, a careful and proper selection for the best treatment is paramount.

Dydrogesterone was proven to be effective to reduce the odds of miscarriage after the treatment in patients with recurrent miscarriages (Carp, 2015). Hence, this study aimed to prove that dydrogesterone was also effective in treating threatened

miscarriage. The composition of dydrogesterone is similar to the activity of progesterone, which has been used widely to treat progesterone deficiency especially related to miscarriage and enhanced oral availability compared to progesterone (Czyzyk et al., 2017). It is also possessed a high selectivity for the progesterone receptor with approximately 5.6 times higher bioavailability than that of progesterone (Mirza et al., 2016).

Dydrogesterone does not bind to androgenic receptors, which reduces the risk of masculinization of female foetuses and does not have androgenic side effects in the mother such as hirsutism and acne (Czyzyk et al., 2017). A large number of reported prospective studies and meta-analyses for almost 3 decades ago has proven the safety of dydrogesterone usage in pregnancy, which showed no incidence of teratogenic effects (Katz et al., 1985; Raman-Wilms, 1995) and not associated with any congenital abnormalities and incidence of low birthweight (Li et al., 2020; Mirza et al., 2016).

2.2 ROUTES OF ADMINISTRATION AND DOSAGE

A recent meta-analysis studied the influence of oral dydrogesterone and vaginal progesterone on threatened miscarriage showed that oral dydrogesterone was better than other routes of administrations and more effective in preventing miscarriages (Lee et al., 2017). Oral administration of dydrogesterone also has better tolerability, compliance, and generally the most acceptable route among the patients (Choudhary et al., 2014; Mirza et al., 2016).

Coomarasamy et al. (2016) conducted a randomized controlled trial to determine whether the treatment via vaginal progestogen would increase the rates of live births and newborn survival among women with unexplained recurrent miscarriage. The result showed that progesterone therapy in the first trimester of pregnancy did not show any

significant increase in the rate of live births among women with unexplained recurrent miscarriage history. Next, Coomarasamy et al. (2019) further compared the incidence of live births after at least 34 weeks of gestation, and the treatment with progestogen resulted in no significant differences (p>0.05) of 75% incidence compared to the placebo group of 72%, (RR 1.03; 95% CI, 1.00 to 1.07; p=0.08). Both of these studies used a vaginal preparation of progesterone at a dose of 400 mg twice daily, and there was a possibility that the results obtained were not similar to women receiving different doses and preparations by other routes of progesterone.

Different dosage of oral dydrogesterone was given in different studies. Wahabi et al. (2018) initially reported a Cochrane review in 2007 and updated in 2018, which studied 6 out of 7 randomized trials of different regimens of progestogen involving women with bleeding at early pregnancy. The study reported a significant risk reduction of miscarriage among patients with the first trimester threatened miscarriage after progesterone treatment as compared to those receiving placebo or conservative treatment (OR 0.64; 95% CI, 0.47 to 0.87).

The recommended dosage of dydrogesterone tablet for the treatment of threatened miscarriage reported by Malaysia Ministry of Health Medicines Formulary in March 2016 is 40 mg at once then 10 mg 8 hourly until symptoms remit. Two previous studies conducted in Malaysia also used similar dosage of dydrogesterone, which were 40 mg at once or 20 mg per day until 16 weeks (Pandian, 2009) and 40 mg at once or 20 mg per day until the bleeding stopped or for 1 week (Omar et al., 2005). Based on this information, a similar dosage was used for the intervention group in this study.

2.3 MISCARRIAGE AND CURRENT MANAGEMENT

Bed rest is the most commonly used conventional treatment for threatened miscarriage. However, a Cochrane review on management with bed rest during pregnancy for preventing miscarriage concluded that there was little evidence related to this topic. There were also many potential side effects related to bed rest (Aleman et al., 2005). In addition, no differences were reported on the risk of miscarriage between the bed rest and the non-bed rest groups, as well as the bed rest in a hospital versus the bed rest at home groups (Aleman et al., 2005).

Uterine muscle relaxant drugs such as beta-agonists are one of the treatments for threatened miscarriage. The beta-agonists act as a muscle relaxant for the uterus and reduce the potential outcome for miscarriage. Lede and Duley (2005) reported a reduced risk of miscarriage and stillbirth among beta-agonist group (RR 0.25, 95% CI, 0.12-0.51), however, there was no difference in terms of pregnancy complications such as preterm birth.

Another treatment for threatened miscarriage is HCG treatment. It is a safe treatment with no reported adverse effects on the mother or baby. In contrast, based on a meta-analysis review, there was no significant difference between groups that received treatments with HCG and no HCG in the miscarriage incidence. However, the limitation of the reported study was poor methodological quality in one of the trials. Hence, better quality research is required in the future to assess the effect of HCG on miscarriage (Li et al., 2017).

A traditional complementary medicine such as acupuncture has provided beneficial effect as a treatment of threatened miscarriage. Magarelli et al. (2009) conducted a study that involved 34 women who received acupuncture treatment after *in-vitro* embryo transfer treatment, which reported a significant reduction in miscarriage

rates. However, acupuncture is still not widely used and accepted as a treatment for threatened miscarriage (Betts et al., 2016; Li et al., 2017)

Among the treatments of threatened miscarriage, oral dydrogesterone has been widely accepted as a safe treatment and more effective than standard care. A systematic review study on dydrogesterone therapy given to patients with threatened miscarriage has shown a reduction in the odds of having a miscarriage by 47% as compared to conservative treatment, with an absolute decrease by 11% of the miscarriage incidence. However, this was an old study conducted 8 years ago (Carp, 2012). Among the six trials conducted in the study, two of them did not state the exclusion criteria and one study was a non-randomized controlled trial. All of them had different regimen and duration of oral dydrogesterone.

Thus, this study was conducted to assess the efficacy of oral progestogen in the first trimester threatened miscarriage based on the number of miscarriages by 20 weeks of gestation in women given oral progestogen therapy compared to conservative therapy in order to. Oral progestogen was selected as it has better tolerability as well as compliance than vaginal preparations. Furthermore, this study has a larger sample size as compared to previous studies conducted in Malaysia.

2.4 RECENT ADVANCE IN MANAGING THREATENED MISCARRIAGE

As progesterone is a potent immunomodulator that may cause immunotolerance in pregnancy, it is reasonable to investigate the role of progesterone supplement in threatened miscarriage as a potential treatment. Recently, Carp (2019) reported that immunotherapy using four immunomodulatory agents, namely paternal leukocyte immunization, intravenous immunoglobulin (IVIg), intralipid, and filgrastim was not proven effective in recurrent pregnancy loss to improve the live birth rate in an

unselected population. In contrast, the immunotherapy was effective when the selected population was a poor prognosis or immune phenomena (Carp, 2019).

To the best of our knowledge, no recent research was reported regarding immunotherapy in treating threatened miscarriage in low-risk population (without any history of recurrent pregnancy loss). Hence, treatment modalities for threatened miscarriage using immunomodulation may be beneficial. For example, aspirin is used for its anti-inflammatory mechanism, anti-coagulants for their anti-inflammatory and anticoagulant mechanisms, and steroids for their anti-inflammatory effects. Some of the expected post-treatment issues include no definitive biomarker to predict which patient suitable and positively responds to immunotherapy for threatened miscarriage. Furthermore, the success rate of immunotherapy especially using immunomodulatory agents in treating threatened miscarriage, cost-effectiveness as well as feasibility require further evaluation.

CHAPTER THREE

METHODOLOGY

3.1 ENROLMENT, TREATMENT ALLOCATION AND ANALYSIS

This prospective observational study has been conducted at the gynaecology ward and Early Pregnancy Assessment Unit (EPAU) in two hospitals: which were Hospital Sultanah Nur Zahirah (a general state-run) and Sultan Ahmad Shah Medical Centre (SASMEC), Kuantan, Pahang (a teaching hospital). It was conducted for 10 months, from June 2019 until March 2020. It involves pregnant women with threatened miscarriage of less or equal to 12 weeks of gestation, who fulfilled inclusion criteria and informed consent.

The sample size was calculated via Power and Sample 3.1.2 software (Dupont and Plummer, 1990). Using this software, the setting was put for 5% level of significance and 80% power with a one-to-one recruitment ratio. It was necessary to recruit 100 subjects for each trial arm, and the number increased up to 120 considering 20% drop up rate. However, due to pandemic situation and movement control order, the number of subjects for interventional group and control group was only 97 and 120, respectively (Figure 3.1).