

**REVIEW OF THE PREGNANCY OUTCOME OF
MOTHER WITH ADVANCED MATERNAL AGE
IN HOSPITAL SULTANAH AMINAH, JOHOR BAHRU
FROM 2017-2018**

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THE REQUIREMENT FOR DEGREE OF MASTER OF
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Tan Yi Ping

1.4 LIST OF ABBREVIATION

AMA	advanced maternal age
HSA	Hospital Sultanah Aminah
IQR	median
JB	Johor Bahru
MREC	Medical Research and Ethics Committee
MRN	Medical Record Number
MOH	Ministry of Health Malaysia
NICU	Neonatal intensive care unit
NMRR	National Medical Research Review
RR	Relative risk
Std.	Standard
X ²	Chi square

1.5 ABSTRAK

Objektif: Kajian ini bertujuan untuk menyiasat kesan terhadap kehamilan di kalangan ibu lanjut usia (umur 35 tahun dan ke atas).

Metodologi: Kajian berbentuk 'cross sectional' ini membandingkan 239 orang ibu berumur 35 tahun dan ke atas dengan 239 orang ibu mengandung umur 20-34 tahun (kumpulan kawalan) yang bersalin di Hospital Sultanah Aminah, Johor sepanjang tahun 2017 dan 2018. Kedua-dua kumpulan ini dianalisis lagi bergantung kepada 'parity' ('nulliparity' dan 'multiparity'). Latar belakang demografi dan hasil kehamilan dibandingkan antara kumpulan.

Keputusan: Umur purata kumpulan kajian dan kumpulan kawalan adalah 37.48 ± 2.226 tahun dan 28.21 ± 3.610 tahun. Ibu mengandung yang berumur lanjut dikaitkan dengan pariti yang lebih tinggi dan menghadapi penyakit perubatan. Umur ibu yang berumur lanjut dikaitkan dengan kejadian anemia yang lebih tinggi. Ibu berumur lanjut yang bersalin buat kali pertama akan meningkatkan risiko pendedahan kepada 'low Apgar score' (≤ 4 pada 1 minit) sebanyak 14.75 berbanding Kawalan. Tiada perbezaan ketara antara kedua-dua kumpulan dalam masalah semasa mengandung dan hasil perinatal yang lain.

Kesimpulan: Kesan kehamilan di golongan ibu berumur lanjut ke atas dirinya dan perinatal dalam kajian ini secara keseluruhannya adalah baik. Terdapat perkaitan rapat di antara anemia dan umur ibu yang berusia dan 'Apgar score' yang rendah pada 1 minit adalah 'independent risk factor' untuk ibu berumur lanjut yang bersalin buat

kali pertama. Kesimpulannya, kajian menunjukkan kandungan/ kehamilan di kalangan ibu lanjut usia adalah setanding kandungan kumpulan kawalan dengan adanya penjagaan antenatal yang baik.

Kata kunci: *Kehamilan, Kesan, Ibu berumur lanjut*

1.6 ABSTRACT

Objective: To investigate the association between advanced maternal age and adverse pregnancy outcomes.

Study method: A cross-sectional study comparing 239 advanced maternal age mother (≥ 35 years old) and a control group of 239 pregnant mothers aged 20–34, delivering at Hospital Sultanah Aminah in Johor from 2017 through 2018. Each of these groups was further analysed depending on parity (nulliparity and multiparity). Demographic background and pregnancy outcomes were compared between the groups.

Result: The mean age of study group and Controls was 37.48 ± 2.226 years and 28.21 ± 3.610 years, respectively. Advanced maternal age was associated with higher parity and pre-existing medical illness. Advanced maternal age was significantly associated with higher incidence of anaemia. Those nulliparity mother with advanced maternal age had increased risk of exposure to lower Apgar scores (≤ 4 at 1 minute) by 14.75 compared to Controls. There were no significant differences between the two age groups in the incidences of other adverse obstetric outcomes and perinatal outcomes.

Conclusion: We observed that maternal anaemia was associated with advanced maternal age and a low Apgar score at 1 minute is an independent risk factor for advanced maternal age nulliparity. Otherwise, this study demonstrated that the the reproduction beyond the age of 35 years is not associated with any significant maternal, delivery and perinatal complications. Overall, the study showed that the

outcome of pregnancy with advanced maternal age is comparable to the control group.

Keywords: *Pregnancy, Outcomes, Advanced maternal age*

2.0 INTRODUCTION AND LITERATURE REVIEW

Advanced maternal age is generally held to signify maternal age after 35 years at the time of delivery. It is a term that implies decreased fertility, and increased risk of maternal as well as perinatal morbidity and mortality. The Council of International Federation of Gynecology and Obstetrics (FIGO) defined advanced maternal age as women age 35 years and older during her pregnancy. They recommended age 35 years as the upper limit.

The past decades have seen a steep rise in the proportion of advanced-age maternity among all births in the Western world, and in the number of advanced-age primigravida in particular.[1,2] Such an increase in maternal age has also been observed in many Asia countries including Malaysia.[3-6] In 2016, using the data from the National Obstetrics Registry (NOR), 26047 cases of deliveries at age of 35 or older were reported from 14 general hospitals in Malaysia. This figure can be translated to 18.42% of total deliveries or 184 per every 1000 deliveries which shown an increment of 2% from the year 2011 (16.4%).

Social trends have encouraged women to delay their first pregnancies until the late 30s and 40s of age. This trend is due to several changes, including women married later in life, the pursuit-by women-of higher education and career advancement, combined with easily accessible contraceptive techniques. Nonetheless, with the advancement of assisted reproductive technologies (ART) and obstetric care, women are able to get pregnant at a later age.

Advanced maternal age has been regarded as a risk factor for complications in pregnancy. Prior studies have reported that increasing maternal age is relevant to risks for various complications including pre-eclampsia, gestational diabetes mellitus, stillbirth, preterm birth, and caesarean delivery.[7,8,9,10] However, some studies have yielded inconsistent conclusions about the outcomes adversely affected by maternal age.[11,12] Thus, the effect of maternal age on adverse outcomes be still controversial.

Additionally, there is limited consensus among studies as to the precise maternal age when the increase in the risk of adverse pregnancy outcome becomes clinically important. Some studies have reported that the association only becomes significant at age greater than 40 years while others suggest that age ≥ 35 years is the cut-off for an increased risk.[13,14,15]

2.1 PREVALENCE AND SOCIO-DEMOGRAPHIC BACKGROUND

Over the past decades, there has been a drastic increase in the number of women having their babies at age 35 and older. Today, according to data from the US National Center for Health Statistics (NCHS), 15% of birthing mothers giving birth are 35 and older, increased from 11% in 2002 and 8% in 1990.[1] There has also been an increase in the number of first babies born to women who are 35 or older. The average age of first-time mothers, in the U.S., increased from 21.4 years to 26.3 years between 1970 and 2014. In the UK, a similar trend has been observed, with statistics showing that between 1987 and 2008 maternity in women aged 35 or over rose from 8% to 20%, and maternity in women aged 40 years or older trebled from 1.2% to 3.6%.[2] Such an increase in maternal age has also been observed in many Asia countries, such as Japan, China, and Taiwan.[3-5]

2.2 IMPACT OF ADVANCED MATERNAL AGE PREGNANCY

There are numerous studies done previously to assess the effect of advanced maternal age on pregnancy outcome, but the results varied. Thus, the pregnancy outcomes related to advanced maternal age and their significance remain debatable.

The association of advanced maternal age and increased risk of congenital anomaly, spontaneous miscarriage, perinatal mortality, and maternal complications have been reported in many studies. Older pregnant people are commonly related to certain chromosomal disorders. For example, Down syndrome happens when there is an extra copy of Chromosome 21. The rate of having a baby with Down syndrome increases with the mother's age, from 1 in 1340 and 1 in 353 at age 25 and 35 respectively, to 1 in 85 at age 40, and 1 in 35 at age 45. The rate of spontaneous miscarriage increases gradually with age, from a 9% miscarriage rate among 22-year old to ~18% among 30 years old, ~20% at age 35, ~40% at age 40, and 84% at age 48.

Large cohort studies, population registry studies, and a large meta-analysis all support a reasonably strong independent association of advancing maternal age with gestational diabetes mellitus (GDM), with the meta-analysis reporting that women in the 35-39 years group have nearly twice the risk and the over 40 years group nearly four times the risk of younger women. [8-15]

A study by Yogeve et al. observed the incidence of gestational diabetes mellitus (GDM) is 3- to 6-fold higher in gravid women over the age of 40 years. Specifically, the prevalence of GDM is ~3-6% in the general population, 7-12% in women over 40

years old, and rises to as high as 30% in gravid women aged >50 years. Other variables like the rates of cesarean delivery, placenta praevia, postpartum hemorrhage, and the adverse neonatal outcome are significantly higher among elderly mothers too.[17]

Jolly et al. in their study concluded that pregnant women ≥ 35 years old are at increased risk of complications in pregnancy compared with younger age group mothers. Most risks, for example, gestational diabetes mellitus, placenta previa, preterm labour, and low birth weight as well as elective caesarean section and operative vaginal delivery rates, were found to be higher among women of advanced maternal age.

In Huang's systematic review on 'maternal age and risk of stillbirth', 24 out of 31 studies found that older women are more likely to have a stillbirth than younger women. When they only looked at studies from developed countries, the risk of having a stillbirth was about 1.2 to 2.23 times higher among older women when compared to younger women.[26]

In 2006, Reddy et al. in their study noted that rates of stillbirth are higher for everyone who is having their first baby compared to subsequent babies, no matter the mother's age. But the rates are even higher in first-time moms who are also 35 or older. Additionally, pregnant mothers more than 40 years old and have given birth before, have a lower stillbirth risk than those giving birth for the first time that is under the age of 35.

Jahromi and Husseini from Iran, in the issue of the Taiwanese Journal of Obstetrics and Gynecology, presented a case-control study to compare the pregnancy outcome of women aged 40 years and older with those at 20–30 years of age. The authors found that the prevalence of gestational hypertensive diseases, abruptio placenta, preterm birth, cesarean delivery, and a low Apgar score at 5 minutes of age was significantly higher in women aged 40 years or older than the control group.[27] This finding confirms with studies on Asian women of advancing age [4,5,24]. They also found that preterm birth and low birth weight (<2,500g) happened more frequently in primiparous older women, while preeclampsia and placental abruption happened more frequently among multiparous older women.

3.0 JUSTIFICATION OF STUDY

There has been a drastic increase in women who get pregnant at age 35 and above in our community. Previous literature has associated these groups of mothers with a high-risk pregnancy with an association with adverse pregnancy outcomes to both the mother and baby. This study aimed to look specifically into these groups of women, looking into their association with maternal, delivery, and perinatal outcomes compared to the control group.

4.0 OBJECTIVES

4.1 GENERAL OBJECTIVES

To evaluate the pregnancy outcome of the mother with advanced maternal age delivered in Hospital Sultanah Aminah, Johor Bahru from 2017 to 2018.

4.2 SPECIFIC OBJECTIVES

1. To evaluate the socio-demographics of the mother with advanced maternal age delivered in Hospital Sultanah Aminah, Johor Bahru.
2. To compare the maternal and perinatal outcomes of advanced maternal age (≥ 35 years old) with a control group (age 20 - 39).
3. To evaluate the impact of parity on pregnancy outcomes in pregnancies complicated by advanced maternal age.

5.0 METHODOLOGY

5.1 STUDY DESIGN, SETTING AND DURATION

This is a cross-sectional study that was conducted in the Department of Obstetrics and Gynaecology of Hospital Sultanah Aminah, Johor Bahru. It is a tertiary hospital and managing both low-risk and high-risk pregnancies, other than being the state referral center. This study was carried out from 2017 till 2018.

5.2 STUDY PARTICIPANTS

This study was conducted among women age 35 years and above who delivered in Hospital Sultanah Aminah, Johor Bahru from 2017 till 2018.

5.3 INCLUSION AND EXCLUSION CRITERIA

5.3.1 INCLUSION CRITERIA

1. Mothers aged 35 years old or older at the time of delivery
2. Viable pregnancy (22 gestational weeks and above)

5.3.2 EXCLUSION CRITERIA

1. Incomplete data e.g. no documentation of needed data
2. Immigrants

5.4 SAMPLE SIZE CALCULATION

Pregnancy outcomes	P0 Adult group	P1 advanced maternal age group	Sample size per arm
Pre eclampsia <i>Muhammad Fakhri Ali et al. (2017)</i>	12.9%	27.1%	137
Gestational diabetes mellitus <i>Rajmohan Laxmy et al. (2013)</i>	3.3%	10.5%	175
Fetal growth restriction <i>Rajmohan Laxmy et al. (2013)</i>	0.3%	28.0%	33
Preterm labor <i>Rajmohan Laxmy et al. (2013)</i> <i>Pawde et al. (2014)</i>	5.0% 10.3%	24.1% 17.5%	52
Stillbirth <i>Rajmohan Laxmy et al. (2013)</i>	0.3%	15.7%	48

The sample size was calculated using PS software version 3.1.2, assuming a 5% precision, 80% of power, and a 1:1 ratio of subject number in two arms.

After accounting for a 30% dropping rate, the calculated sample size is 239 pregnant mothers age more than 35.

Thus, the final sample size that recruited for this study is 239 for pregnant mother age more than 35 and another 239 for the controlled group (age 20 to 34 years)

5.5 SAMPLING METHOD

All patients who delivered in Hospital Sultanah Aminah from 2017 to 2018 and fulfilled the criteria were selected from the hospital birth registry book. Simple random sampling was done using computer-generated random number table. The patients' medical record was traced and reviewed.

The data was recorded in research proforma (Appendix 1). All the data elaboration was analyzed and edited by SPSS version 26.0.

5.6 RESEARCH TOOL

Research proforma was used to collect data from the patient's medical record which included the following area:

1. Social-demographic profiles of the respondents included ethnicity, occupation, education level, body mass index, gestation weeks at the first visit and parity status; pre-existing medical illness and assisted reproductive treatment
2. The adverse pregnancy outcomes were divided into maternal, delivery and fetal outcomes.
 - i. Adverse maternal outcomes included pregnancy-induced hypertension, pre-eclampsia, and gestational diabetes mellitus, and anaemia in pregnancy.

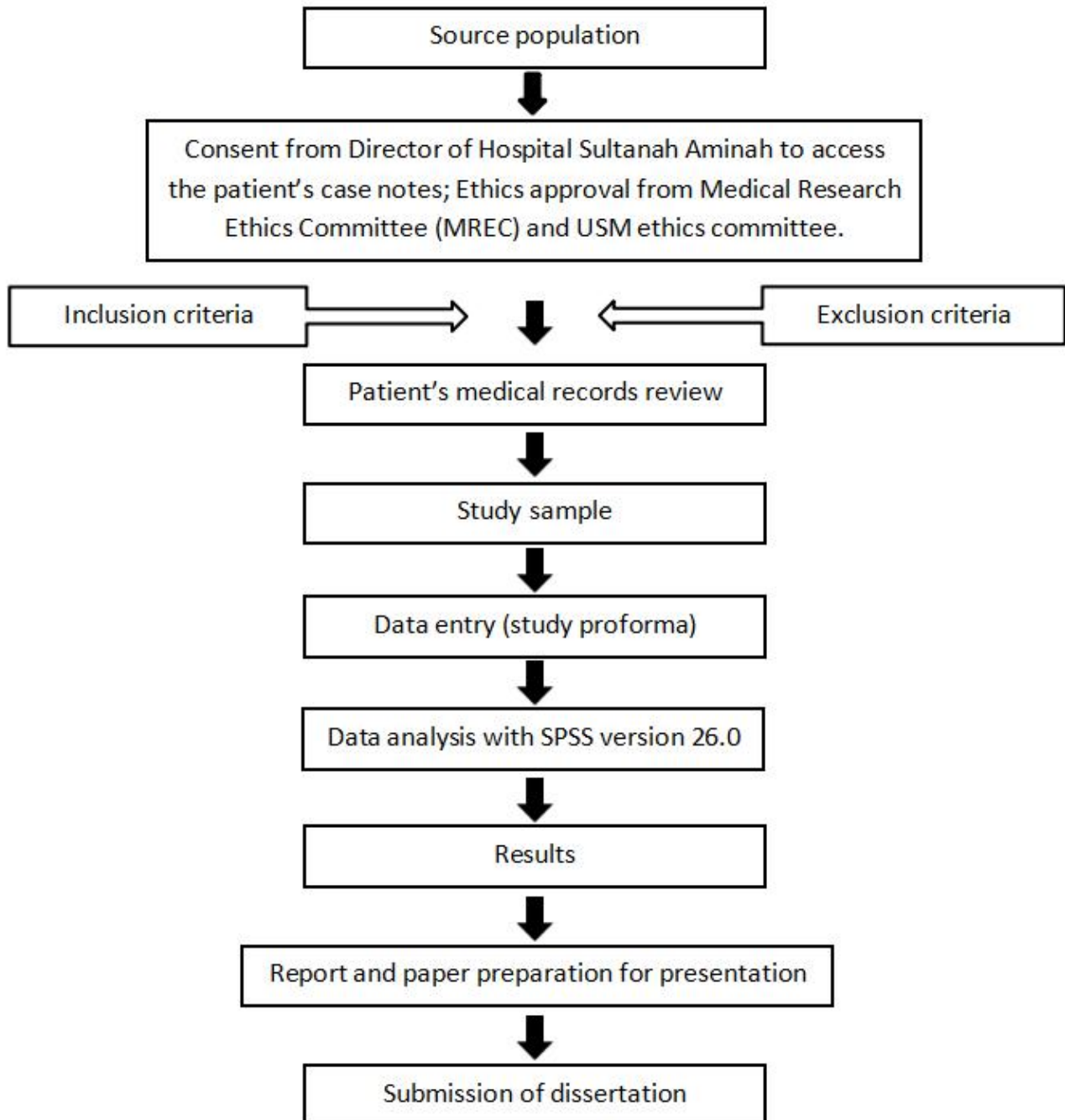
- ii. Delivery outcomes included induction of labour and types of delivery.
- iii. Adverse perinatal outcomes consisted of prematurity, low or high birth weight, Apgar score, stillbirth/ early neonatal death, NICU admission, chromosomal abnormality and major fetal abnormalities (e.g. congenital heart disease, spinal bifida, gastrointestinal anomaly)

(Appendix 1)

5.7 DATA COLLECTION METHOD

The ethical approval was obtained from the Medical Research Ethics Committee (MREC) and the USM ethics committee. Consent from the Director of Hospital Sultanah Aminah was obtained to get access to the case notes. The hospital birth registry record was reviewed to identify patients for the study. Patient's record was subsequently traced from the record office. The records were reviewed and the patient's information was documented in the patient's clinical form. The data was collected and analyzed.

5.8 STUDY FLOW CHART



5.9 STATISTICAL ANALYSIS

Data entry and analysis was performed using IBM SPSS Statistics Data Analyzer version 26.0 licensed to Universiti Sains Malaysia.

For this analysis, mothers aged 20-34 years of age at the time of delivery represented the reference group/ control group.

Descriptive statistics were used for maternal demographic, inter-current medical illness, and pregnancy outcomes in relation to the maternal age groups. Numerical data were presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data were presented as frequency (percentage). Chi square/ Student's t-test was used to determine the statistically significant differences between the variables.

A logistic regression model was used to analyse the association between each advanced maternal age group and each adverse outcome. Multinomial logistic regression was used for dependent variables with more than 2 outcomes such as delivery outcomes, birth weights and gestation at births.

5.10 ETHICAL CONSIDERATION

This study was conducted after obtaining ethics approval from the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia via the National Medical Research Registry (NMMR). Since this study was extracting secondary data from an existing database without identifying the individual patient, the study team was requested for the waiver of informed consent from MREC.

1. Declaration of conflict of interest

This study was investigator-initiated research in which there was no financial arrangement or employment by any sponsor or product manufacturer. It was self-funding without any payment of other sorts from the sponsor or product manufacturer to support the activities of the investigators. There was no propriety interest or equity interest in product manufacturer or any commercial organization involved in this study. Thus, there was no conflict of interest for this study.

2. Privacy and confidentiality

Patients' identity was kept confidential by using subject ID without disclosure of patients' details such as name or registration number. All data were collected as in the data collection sheet using the subject ID and was saved in soft copy in computer and protected with a password. Data was only reviewed by the researcher and team and was kept in a locked office. Data will be discarded after 3 years of completion of this study. Personal information and study data were not revealed to the subjects.

3. The researcher has adhered to the principles of the Declaration of Helsinki and the Malaysia Good Clinical Practice Guidelines.

4. Ethical review board approval

a) National Medical Research Review (NMRR), MOH

(NMRR-19-3861-51572)

b) Human Medical Research and Ethics Committee of USM

(USM/JEPeM/19110834)

(Appendix 3)

5. Community sensitivities and benefits

There has been drastic increase in women who get pregnant at age 35 and above in our community. This study aims to provide local data of advanced maternal age pregnancy and also related complication in the local population which can aid in the management of advanced maternal age pregnancy in our local population.

6. Publication policy

All the information obtained from this study will be kept confidential and only summarized data will be presented in reports or publications. No subject will be identified in any form of verbal or writing presentation and publication.

6.0 MANUSCRIPT

This manuscript was written in accordance with the submission guideline for the Malaysian Journal of Medical Sciences (ISSN 1394-195X, online- ISSN 2180-4303).

(Appendix 4)

**Review of The Pregnancy Outcome of Mother with Advanced Maternal Age in
HSA, JB (2017-2018)**

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ABSTRACT

Objective: To investigate the association between advanced maternal age and adverse pregnancy outcomes.

Study method: A cross-sectional study comparing 239 advanced maternal age mother (≥ 35 years old) and a control group of 239 pregnant mothers aged 20–34, delivering at Hospital Sultanah Aminah in Johor from 2017 through 2018. Each of these groups was further analysed depending on parity (nulliparity and multiparity). Demographic background and pregnancy outcomes were compared between the groups.

Result: The mean age of study group and Controls was 37.48 ± 2.226 years and 28.21 ± 3.610 years, respectively. Advanced maternal age was associated with higher parity and pre-existing medical illness. Advanced maternal age was significantly associated with higher incidence of anaemia. Those nulliparity mother with advanced maternal age had increased risk of exposure to lower Apgar scores (≤ 4 at 1 minute) by 14.75 compared to Controls. There were no significant differences between the two age groups in the incidences of other adverse obstetric outcomes and perinatal outcomes.

Conclusion: We observed that maternal anaemia was associated with advanced maternal age and a low Apgar score at 1 minute is an independent risk factor for advanced maternal age nulliparity. Otherwise, this study demonstrated that the the reproduction beyond the age of 35 years is not associated with any significant maternal, delivery and perinatal complications. Overall, the study showed that the

outcome of pregnancy with advanced maternal age is comparable to the control group.

Keywords: *Pregnancy, Outcomes, Advanced maternal age*

INTRODUCTION

Advanced maternal age is generally held to signify maternal age after 35 years at the time of delivery. It is a term that implies decreased fertility, and increased risk of maternal as well as perinatal morbidity and mortality. The Council of International Federation of Gynecology and Obstetrics (FIGO) defined advanced maternal age as women age 35 years and older during her pregnancy. They recommended age 35 years as the upper limit.

The past decades have seen a steep rise in the proportion of advanced-age maternity among all births in the Western world, and in the number of advanced-age primigravida in particular.[1,2] Such an increase in maternal age has also been observed in many Asia countries including Malaysia.[3,4,5] In 2016, using the data from the National Obstetrics Registry (NOR), 26047 cases of deliveries at age of 35 or older were reported from 14 general hospitals in Malaysia. This figure can be translated to 18.42% of total deliveries or 184 per every 1000 deliveries which shown an increment of 2% from the year 2011 (16.4%).[6]

Social trends have encouraged women to delay their first pregnancies until the late 30s and 40s of age. This trend is due to several changes, including women married later in life, the pursuit-by women-of higher education and career advancement, combined with easily accessible contraceptive techniques. Nonetheless, with the advancement of assisted reproductive technologies (ART) and obstetric care, women are able to get pregnant at a later age.

Advanced maternal age has been regarded as a risk factor for complications in pregnancy. Prior studies have reported that increasing maternal age is relevant to risks for various complications including pre-eclampsia, gestational diabetes mellitus, stillbirth, preterm birth, and caesarean delivery.[7,8,9,10] However, some studies have yielded inconsistent conclusions about the outcomes adversely affected by maternal age.[11,12] Thus, the effect of maternal age on adverse outcomes be still controversial.

Additionally, there is limited consensus among studies as to the precise maternal age when the increase in the risk of adverse pregnancy outcome becomes clinically important. Some studies have reported that the association only becomes significant at age greater than 40 years while others suggest that age ≥ 35 years is the cut-off for an increased risk.[13,14,15]

MATERIALS AND METHODS

The study aimed to investigate the association between advanced maternal age (maternal age 35 years and above) and adverse pregnancy outcomes.

This is a cross sectional study involved women who gave birth in Hospital Sultanah Aminah in Johor, Malaysia over 2 years (2017-2018). The study sample consisted of randomly selected 239 pregnant women who were at least 35 years old at the time of delivery during the study period. The inclusion criteria consisted of (1) singleton pregnancy (2) delivery beyond 22 weeks' gestation or birth weight more than 500 gm. While exclusion criteria were incomplete medical records and immigrants. Because of the intrinsic risk of multiple pregnancies, this study was restricted to singleton pregnancies. For this study, those women at the age of 20 to 34 years, who are usually considered to have the lowest maternal and perinatal morbidity and mortality, formed the control group. The control group was randomly recruited from women giving birth during the same study period with a ratio of 1:1 case to control subjects. We compared the pregnancy outcomes of AMA group vs control group. The ethical approval of this study has been given by National Medical Research Review (NMRR-19-3861-51572) and Human Medical Research and Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/19110834). The research process warranted anonymity and confidentiality by disregarded the respondent's name and used code on the data collection sheet.

Data from the patient's medical record was reviewed and analyzed. This included demographic features, maternal medical conditions, pregnancy complications,