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The effect of advanced maternal age on pregnancy outcomes: A prospective study

Protocol of thesis

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Introduction

Advanced maternal age (AMA) is mostly defined as a pregnancy in women ≥35 years of age or more during their pregnancy or time of delivery (1). It grows trending in high-income countries, which is most commonly seen in older primigravida women who delay child bearing by life style choice or due to underlying subfertility, but also includes multiparous women continuing childbearing. Approximately 18% of all united states birth in 2018 were to women with advanced maternal age compare with approximately 5% before, much of this shift due to delayed first births, the rate of first births increased seven-fold among women aged 35 to 39 y and five-fold among women aged 40 to 44 y between 1985 and 2018 (2).

In England, the incidence of births to women aged 35y increased from 6% to 20% at 2013. Pregnancy at advanced maternal age is associated with different adverse neonatal outcomes. It is associated with stillbirth and also complicated by intrauterine fetal death (IUFD) and neonatal death (3 & 4). Advanced maternal age is reported to be associated with a range of pregnancy complications including: fetal growth restriction (FGR), preeclampsia (PE), placental abruption, pre-term birth (PTB) and stillbirth (5).

Perinatal adverse outcomes like preterm birth, early neonatal death, low birth weight, neonatal intensive care unit (NICU) admission and APGAR score of less than seven at five minutes are significantly associated with pregnancy at advanced maternal age (6). The adverse outcomes result from inadequate cardiovascular adaptation during pregnancy, which impedes the hemodynamic changes for supporting the fetus (7). This may explain occurrence of intrauterine growth restriction and placental abruption at advanced maternal age (8).

Early pregnancy outcomes associated with advanced maternal age include: Ectopic pregnancy which increase a four- to eight-fold in women more 35 years increasing maternal mortality and morbidity (9). Epidemiological studies show an association between advanced maternal and paternal ages and the risk of autism spectrum disorders in the offspring, also advanced maternal age is a risk factor for congenital malformation and Down syndrome (10).

Risk of spontaneous abortion between 6 to 14 weeks of pregnancy increased with increasing maternal age (11). Late pregnancy outcomes including Gestational DM and preeclampsia which increasing up to 10% in women more 40 years of age and higher up to 35% in women more than 50 years of age which may cause intra uterine growth retardation and stillbirth (12).

Advanced maternal age is also linked to a higher prevalence of placenta praevia and placental abruption, both of which cause bleeding in late pregnancy (after about 20 weeks) especially in multipara (13). Women more than 40 years of age showed an eight-fold increased risk of amniotic fluid embolism due to increased incidence of caesarian section and a three-fold increased risk of obstetric shock compared with women age 25–29 years (14).

According to the royal college of obstetricians and gynecologists, the optimum period for child bearing is between 20 and 35 years of age to decrease maternal and neonatal complications (15).

Aim of work

This study to evaluate the effect of advanced maternal age on the outcomes of pregnancy which include: maternal, obstetric, fetal and perinatal outcomes.

Patient and methods

Study Design & Area:

 A prospective cohort study of pregnant women recruited from Department of Obstetrics and Gynecology, Mansoura University Hospitals during **June** 2021 until **June** 2022 and may be extended if needed.

 The hospital operates Antenatal clinics six hours every day except Friday.

 Mansoura University Hospital is Referral teaching hospital, located in Mansoura, Egypt.

Study population:

The study group will be represented by 50 primigravida women aged 35y or more during their pregnancy and the control group will be represented by 50 primigravida women aged 20-34 y during their pregnancy till the time of delivery.

A. Inclusion criteria:

- Primigravida Women with singleton pregnancies aged 20 to 34 years in control group and aged 35 y or more in case group, natural conception or with using ART, who seeking for routine antenatal care to the university hospital and who will accept the study protocol.

B. Exclusion criteria:

- Patients aged less than 20 y will be excluded from the study.
- Patients with medical disorders (antiphospholipid syndrome, chronic hypertension, pre-existing diabetes, autoimmune diseases, thrombo-embolic disease).
- Multipara.

Sample size

Sample size was calculated by PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Based on previous studies including Yogev et al. (2010), the authors hypothesize an overall poor outcome in 20% of young pregnant group vs. 60% in elderly pregnant group with a prevalence of elderly pregnant ladies of 25% vs. 75% of young pregnant ladies.

A logistic regression of a binary response variable (Y) on a binary independent variable (X) with a sample size (N) of 80 observations (of which 50% are in the group X=0 [40 young pregnant ladies] and 50% are in the group X=1 [40 elderly pregnant ladies]) achieves 94% power at a 0.050 significance level to detect a change in Prob (Y=1) from the baseline value of 0.200 to 0.600. This change corresponds to an odds ratio of 6.000.A two-sided Wald test is used.

Considering a possible dropout rate (DR) of 20%, the expected number of dropouts will be 20, and the dropout-inflated enrollment sample size (N') will be 100 participants (50 young, and 50 elderly) where N' = N / (1 – DR).

- We will have 2 groups: the **first** group will be represented by 50 women aged 35 y or more and the **second** group will be represented by 50 women aged from 20 to 34 y.

- **The first group** will be also divided into 2 subgroups: group (1A) aged from 35y to 40 y, the group (1B) aged above 40 y and we will compare between the outcomes in the 2 groups which include maternal, obstetric, fetal and perinatal outcomes.
- We will also compare between those with spontaneous pregnancy and those with ART.

All women in this study will be subjected to the following:

I. History:

a. Personal (age, duration of marriage, educational level, special habits).

b. Menstrual: LMP to detect Gestational age expressed in weeks which calculated from first day of LMP. For patients who underwent in vitro fertilization, gestational age will be calculated from the date of the embryo transfer.

c. Obstetric history: all patients will be primigravida.

d. Past history: of any medical disease or surgical operation.

e. Family history: of any hereditary or non-hereditary disease.

c. Present history: of any symptoms during pregnancy, analysis of any complain, investigations will be done and treatment will be given during pregnancy.

II. Clinical examination: General, abdominal and local examination.

General examination: include blood pressure, pulse, temperature, height and weight to calculate body mass index (BMI) to determine maternal obesity.

- Blood pressure to exclude the hypertensive patients. We will measure blood pressure in each antenatal visit to diagnose the cases which may develop gestational hypertension or preeclampsia after 20 weeks of gestations which will be screened and diagnosed clinically by the obstetricians, according to guidelines (16).

Abdominal examination: include obstetric grips.

Local examination: when indicated.

III. Investigations:

- All pregnant women will undergo routine investigations at the first antenatal visit which include: CBC, RH grouping, blood grouping, urine analysis, fasting and postprandial blood glucose.

-All pregnant women will be screened for gestational diabetes mellitus (GDM) with a 50-g oral glucose challenge test between 24 and 28 weeks of gestation. Women with abnormal glucose challenge test (140 mg/dL) will undergo a 3-hour oral glucose tolerance test with a 100-g oral glucose load. The diagnosis of GDM will be made when levels of blood glucose are fasting plasma glucose above 95 mg/dL, 1 hour postprandial above 130-140 mg/dL, and 2 hours postprandial above 120mg/dL according to The American College of Obstetricians and Gynecologists (ACOG) recommendations (17).

- All pregnant women will undergo a monthly ultrasound examination until delivery.

- All obstetrical and clinical data will be recorded and collected in an appropriate database.

-Obstetric outcomes will be recorded regarding pregnancy induced hypertension, gestational diabetes mellitus (GDM), anemia, antepartum hemorrhage, oligohydraminos or polyhydraminos, obtetretric shock and intrapartum hemorrhage.

-Maternal outcomes will be recorded regarding mode of delivery “ceaserean or vaginal delivery”, premature rupture of membranes, preterm birth which is defined as delivery of an infant before 37 weeks of gestation and will be classified into late preterm (from 34 to less than 37 weeks of gestation) and early preterm birth (delivery from 28 to 34 weeks of gestation), obstructed labor and prolonged labor.

-Fetal outcomes will be recorded regarding congenital malformations, intrauterine growth restriction, intrauterine fetal death and stillbirth.

- Perinatal outcomes will be recorded regarding birth weight which will be classified into low birth weight (less than 2500 g), very low birth weight (less than 1500 g) and macrosomia (more than 4000 g), birth asphyxia, meconium aspiration syndrome, NICU admission, neonatal hypoglycemia, Hyperbilirubinemia, 5-Min Apgar score less than 7 and neonatal death.

Ethical Consideration

- Agreement for this study will be obtained from the hospital's ethical committee.
- Study protocol will be submitted for approval by IRB.
- Informed consent will be obtained from pregnant women after adequate provision of information regarding the study requirements and purpose.
- Personal privacy will be respected in all levels of the study. Collected data will not be used for any other purpose.

Statistical analysis

Data will be entered and analyzed using IBM-SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.)

Qualitative data will be presented as Number and percent, Quantitative data will be tested for normality using Shapiro-Wilk’s test then described as mean and standard deviation for normally distributed data and median and range for non-normally distributed. The appropriate statistical test will be applied according to data type with the following suggested tests: Chi-Square for categorical variable.

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