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Abstract: Objective: Advanced maternal age (AMA) is associated with increased risk for preeclampsia, however, paucity of data exists regarding the characteristics of the disease in this age group. Our aim was to determine the characteristics and severity of preeclampsia as compared between older and younger gravidas.
Study Design: A retrospective case controlled study in single tertiary care center of women diagnosed with preeclampsia. Nulliparous women ≥40 years old with singleton pregnancies ≥ 24 0/7 weeks' gestation were matched (1:2 ratio) with young (20-34 years old) nulliparous women.
Results: Rate of severe preeclampsia (60.9 vs 69.6% respectively), HELLP, eclampsia or need for magnesium treatment did not differ between the groups. However, AMA group had increased rate of post-partum presentation or exacerbation of preeclampsia compared to controls (50.0 vs. 28.3% respectively, p=0.01). 93.5% of AMA group had cesarean section (CS) compared to 52.2% of controls (p<0.0001). There was no difference in birthweight, rate of small for gestational age or composite neonatal morbidity between the groups.
Conclusions: Preeclampsia at advanced maternal age carries similar rate of severe preeclampsia and complications compared to young women. However, women more than 40 years old have increased risk for presentation or exacerbation of preeclampsia in the post-partum period and increased rate of CS compared to younger gravidas.

Characteristics and severity of preeclampsia compared between young and elderly gravidas with hypertensive disease

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Introduction: Advanced maternal age (AMA) is associated with increased risk for preeclampsia, however, paucity of data exists regarding the characteristics of the disease in this age group. Our aim was to determine the characteristics and severity of preeclampsia as compared between older and younger gravidas.

Materials & Methods: A retrospective case controlled study in single tertiary care center of women diagnosed with preeclampsia. Nulliparous women ≥40 years old with singleton pregnancies ≥ 24 0/7 weeks' gestation were matched (1:2 ratio) with young (20-34 years old) nulliparous women.

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Conclusions: Preeclampsia at advanced maternal age carries similar rate of severe preeclampsia and complications compared to young women. However, women more than 40 years old have increased risk for presentation or

exacerbation of preeclampsia in the post-partum period and increased rate of CS compared to younger gravidas.

Introduction

Childbirth at advanced maternal age (AMA) has become increasingly common in developed countries.[1-4] Women are postponing child baring to fulfill their social, economic and professional aspirations.[3,5-8]

The mean maternal age of first born child in Israel increased over the last decades from 25 in 1994 to 27.5 years old in 2015. Over the past 5 years there was an 8% increase in deliveries among women aged 40 to 44, and 2% increase among women aged 45 or older. In 2015, 3% of women who gave birth were older than 41.[9]

Pregnancy at AMA is known to be associated with increased risks, including: miscarriage, stillbirth, preeclampsia, gestational hypertension, gestational diabetes mellitus, small for gestational age and preterm birth.[10-25] AMA is additionally associated with higher rates of operative deliveries and caesarean sections.[20, 26-29]

The risk for preeclampsia is increased at the advanced maternal age. Women aged 40 or older have a twofold rate of preeclampsia compared to the general population,[30] oocyte donation commonly used for AMA, is associated with as high as 25% risk of preeclampsia.[31-34]

The increased prevalence of preeclampsia in AMA is well described, However, there is scarcity of data regarding the severity and the characteristics of hypertensive disease of pregnancy in this age group.

Pre-eclampsia with severe features may lead to intra uterine growth restriction as well as iatrogenic preterm labour. Hence exposing the fetus to complications of prematurity, associated with severe morbidity, handicap and even perinatal death.[35, 36] Exacerbation of the disease during pregnancy or in the immediate post-partum period, may expose the mother to life-threatening adverse events, such as placental abruption, eclampsia, consumption coagulopathy, acute respiratory distress syndrome, acute renal failure, subcapsular liver hematoma and even maternal death.[37] Moreover, preeclampsia foretells increased risk for cardiovascular and metabolic disease later in life. [38] The diagnosis and treatment of severe preeclampsia is of paramount importance and proper consultation for women at risk is warranted.

We aimed to evaluate the severity and characteristics of preeclampsia in AMA women compared to younger population diagnosed with PET.

Materials and methods

A retrospective cohort study of AMA nulliparous women, who gave birth at one tertiary medical center, between January 1, 2011, and March 30, 2016, and where diagnosed with preeclampsia either pre-partum, during labor, or in the immediate post-partum period.

Women at advanced maternal age ≥40 years old (AMA) were compared in 1:2 ratio to young nulliparous women ≤ 35 years old (YMA).

Inclusion criteria included nulliparity, singleton and non-anomalous pregnancies who delivered at ≥24 weeks of gestation, and where diagnosed with preeclampsia.

Exclusion criteria included multifetal pregnancy, preeclampsia diagnosed prior to 24 weeks, known fetal anomalies.

Gestational age calculation was based on one of the followings: the last menstrual period (LMP), or first-trimester ultrasound examination when the LMP was unavailable or if there was a discrepancy greater than 7 days between the two.

Preeclampsia was defined as a new onset of hypertension, complicated by either proteinuria, end-organ dysfunction or both after 20 weeks of gestation in women who were previously normotensive. Mild preeclampsia was defined as systolic blood pressure (BP) between 140 to 159 and diastolic BP between 90-109, proteinuria of above 300mg but less than 5 gr per 24 hours or urinary test strip of +1 or +2, without any symptoms. Severe features of preeclampsia included: systolic BP greater than 160 mm Hg and or diastolic BP greater than 110 mm Hg, new-onset persistent cerebral symptoms (headaches or visual disturbances), impaired liver function (abnormally elevated liver enzymes), severe and persistent right upper quadrant or epigastric pain, thrombocytopenia (platelet count <100,000/µL) or progressive renal insufficiency (serum creatinine >1.1

mg/dL). During the study period proteinuria of ≥ 5 gr per 24 hr or urinary test strip results of ≥ +3 was one of criteria for severe preeclampsia.

For women diagnosed with chronic hypertensive disease, Superimposed PET was defined as an increase in blood pressure that was previously well controlled, escalation of antihypertensive medications needed to control the blood pressure, new-onset, or an increase in proteinuria as well as occurrence of one of the severe symptoms as defined above.

Data were extracted from a computerized patients' database. We collected information about Maternal demographics, mode of conception (spontaneous versus IVF) and medical history (chronic hypertension and diabetes), maternal morbidity, characteristics of preeclampsia (onset of diagnosis gestational age at delivery and maximal blood pressure values), severe preeclampsia (HELLP, eclampsia and MgSo4 treatment), length of hospitalization and number of medications during hospitalization, intrapartum and post-partum morbidity, as well as mode of delivery.

Newborn characteristics included, birthweight, cord PH, 5-minute APGR score, postpartum complications and length of hospitalization.

Our primary outcome was the severity of preeclampsia. Secondary outcomes included the onset of preeclampsia in relation to pregnancy and delivery. gestational age at diagnosis and delivery, mode of delivery, rate of HELLP, eclampsia, and other severe features as well as neonatal complications such as SGA and composite neonatal morbidity.

Composite adverse neonatal outcome was defined as the presence of one or more of the following: cord PH < 7.1, small for gestational age (SGA), low birth weight, 5-minute APGAR score < 7, neonatal intensive care unit (NICU) admission, respiratory disease, hypotension, intra-ventricular hemorrhage (IVH) and death.

This study was approved by the local Institutional Review Board of the Sheba Medical Center, Tel Hashomer, Israel.

Statistical analysis:

Categorical variables were described as frequency and percentage. Normality of the data was tested using the Kolmogorov–Smirnov test. Significance was accepted at $p < 0.05$. Normally distributed continuous variables were described using mean ± standard deviation while non-normally distributed continuous variables were described using median and interquartile range. Logistic regression analysis was performed including parameters with a $p < 0.05$ in univariate analysis to determine which factors were significantly and independently associated with severe hypertensive disease and presentation or exacerbation of preeclampsia at the post-partum period.

Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (IBM SPSS v.19; IBM Corporation Inc, Armonk, NY, USA).

Results

The study included 46 AMA women aged 43.7±3.4 years old (y.o.) (mean ± Standard deviation) and 92 YMA women aged 28.5±3.7 y.o. who were diagnosed with preeclampsia. 43.5% of the patients in the AMA group conceived with oocyte donation compared to 1.1% of the YMA group (*p<0.0001*). AMA nulliparous gravidas had increased rate of chronic hypertension (30.4 vs. 6.5%, *p<0.0001*) and gestational/ pre-gestational diabetes (26.1 vs. 10.9% respectively, *p=0.03*) compared to controls. (Table 1). Prior to delivery 60.9% of AMA had severe preeclampsia and 39.1% had mild preeclampsia compared to 69.6% and 31.4% respectively in YMA, p=NS. However, in the postpartum period, AMA group had significantly increased rate of severe preeclampsia compared to controls (50.0 vs. 28.3% respectively, *p=0.01*)

The gestational age at diagnosis or delivery was similar for AMA and YMA women (36.0 vs. 35.5 at diagnosis and 37.0 vs. 36.0 at delivery. p=NS). AMA women had elevated maximal mean systolic blood pressure (171.0±14) compared to younger gravidas (160.0±17) (*p<0.0001*). There was no difference in maximal diastolic blood pressure between the groups. No difference was found in the rate of HELLP, eclampsia, need for magnesium sulphate therapy, duration of conservative management and number of antihypertensive medications needed prior to delivery. Among the group of women who exhibited severe postpartum hypertensive disease, AMA gravidas had increased rate of severe blood pressure values compared to controls (43.5 vs. 18.5%, *p = 0.004*) and higher rate of serum creatinine level greater than 1.1 (15.2 vs. 4.3%, *p = 0.042*).

(Table 1) Moreover, AMA group had longer post-partum hospitalization. (6.0 ± 2.2 vs. 5.0 ± 4.1days, *p<0.0001*). (Table 2).

Multivariate logistic regression to predict risk factors for post-partum hypertensive disease was applied to the parameters statistically different between the groups, with p <0.1. Including maternal age, BMI, mode of conception, oocyte donation, GA at diagnosis and delivery, thrombophilia, chronic hypertension, smoking, GDM, HELLP, proteinuria, eclampsia and mode of delivery. Multivariate regression revealed three significant risk factors for post-partum hypertensive disease were found: AMA (OR-3.62, CI 1.56-8.38, *P=0.003*), pre-partum in hospital conservative management for preeclampsia (OR-4.51, CI 1.67-12.17, *P=0.003*) and pre-partum HELLP syndrome (OR-3.46, CI 1.19-10.06, *P=0.022*).

YMA women went much more often through trial of labor (75 vs. 19.6%, *p<0.0001*). 44.5% YMA group had successful spontaneous vaginal delivery, 3.3% had operative vaginal delivery and 52.2% delivered by caesarean section (*p<0.0001*). 85.4% (41/48) of the cesarean sections were urgent and 14.6% (7/48) were elective, (*p=0.08*). In comparison 6.5% of AMA group delivered by spontaneous vaginal delivery, none by operative vaginal delivery and 93.5% delivered by cesarean section. (*p<0.0001*) From all 43 AMA women who delivered by cesarean sections, 29 (67.4%) underwent urgent caesarean section and 14 women (32.6%) underwent elective caesarean section. (*p=0.08*). (Figure 1)

There was no difference in birthweight, rate of small for gestational age or composite neonatal morbidity between the groups. (Table 3)

Discussion

This is the first investigation of the characteristics of preeclampsia compared between young and elderly gravidas before or after the delivery.

Our study results found that advanced maternal age women diagnosed with preeclampsia during pregnancy had more severe hypertensive disease in the post-partum period, elevated rate of severe hypertension following the delivery, increased rate of serum creatinine level above 1.1 mg/dL and longer hospitalization compared to younger women.

Multivariate analysis revealed that, AMA, pre-partum in-hospital conservative management and pre-partum HELLP syndrome were found to be risk factors for post-partum severe hypertensive disease among women with preeclampsia prior to delivery.

However, prior to delivery there was no difference in the severity of the characteristics of preeclampsia between younger and older gravidas, including gestational age at diagnosis and delivery, number of medications needed to control hypertension during pregnancy and duration of conservative management prior to delivery. AMA women did not have more HELLP syndrome, eclampsia or need for Magnesium treatment during pregnancy.

AMA women had almost twofold cesarean sections compared to younger mothers However, there was no significant statistical difference in urgent cesarean sections between the groups.

The association between AMA and severe post-partum preeclampsia was not previously described. There are several possible explanations for the higher rates of severe hypertensive disease following delivery among AMA women.

1. AMA women underwent more cesarean sections than younger women, cesarean sections may be associated with two factors that can contribute to the higher rate of post-partum preeclampsia seen in the AMA group:
    a. Large volume of fluids was given during cesarean sections. In some women, delayed or acute mobilization of large volume of fluid into the intravascular space, particularly in women with suboptimal renal function, can lead to volume overload resulting in hypertension. [42-43].
    b. Nonsteroidal anti-inflammatory drugs (NSAIDS) are given for pain management at the sheba medical center post cesarean section. NSAID such as Ibuprofen are associated with vasoconstriction and sodium and water retention, both of which can result in severe hypertension. [45]
2. AMA women had a much higher rate of chronic hypertension and superimposed preeclampsia compared to YMA (30.4 vs 6.5% respectively in our study). In a study by Peterson et al [44] women with chronic

hypertension had an increased need for postpartum antihypertensive medication.

3. New onset post-partum preeclampsia. Vilchez et al [46] , suggested that new onset postpartum preeclampsia and antepartum preeclampsia may represent different disorders. They defined a specific demographic profile of patients that would most likely develop new-onset postpartum preeclampsia. One of the characteristics was AMA. They suggested that there might be a different pathogenesis of the latter disorder.

Our data is consistent with other studies that have shown higher rates of caesarean sections among older nulliparous gravidas [47-49]. Urgent caesarean sections were seemed to be more frequent in the YMA group than in the study group. (85.4 vs. 67.4%). However, it was not statistically significant. The most reasonable explanation is that many of the older mothers delivered by elective caesarean section without trial of labour, hence, there were less urgent operations in this group. Other studies have shown conflicting data regarding urgent and elective caesarean sections. Rendtorff et al [47] suggested that there is no difference in urgent and elective caesareans in younger compared to older women, Whereas Oakley et al [49] found that older women have increased risk for either urgent or elective operations.

In our study there was no difference in neonatal outcomes between older and younger mothers. No statistical difference was found regarding birth weight, SGA and composite neonatal morbidity. Lack of difference between the groups in

gestational age at delivery and severe features of preeclampsia is expected to predict similar neonatal outcomes as found.

Our study has several strengths: To our knowledge this is the first study that compared the characteristics of preeclampsia in young and elderly gravida. Even though pregnancies at AMA are not frequent, our study was carried out in a tertiary institution, hence, enabled us to evaluate a large group of elderly primigravida with preeclampsia.

Other studies that evaluated the characteristics of preeclampsia compared AMA women to the general population of YMA. We evaluated for the first time two groups of women that all had preeclampsia.

All women were managed in one medical center where women diagnosed with preeclampsia are managed by all physicians in accordance with the same departmental guidelines and protocols leading to minimal deviations in care.

Our study also has limitations:

Women in the AMA group had an increased prevalence of chronic hypertension and most of these women had superimposed PET compared to new onset PET in the YMA group. This may be a major contributor to different characteristics of the disease. However, the lack of difference in severity of PET between the groups prior to delivery alleviates this concern.

There is a possible bias in the attention given to the patients by the physicians since older women are considered at higher risk and that may influence decisions making in regard to mode and timing of delivery. As expected most

AMA women had cesarean section, however their age did not influence the timing of delivery.

Women at advanced maternal age with preeclampsia and their neonates have similar outcomes to YMA women with preeclampsia. however, our study emphasizes the importance of appropriate follow up and diagnosis of preeclampsia exacerbation in the post-partum period for AMA women. Further studies are needed to investigate the basis for the increased risk of post-partum exacerbation of PET in AMA women

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Table 1**. Maternal Characteristics**

Variables	**YMA (n=92)**	**AMA (n=46)**	**P-value**
Age (y.) mean± SD	28.5±3.7	43.7±3.4	<0.0001
BMI (Kg/M^2) mean± SD	30.4±5.6	30.3±5.0	NS
Spontaneous Pregnancy. n (%)	78.0 (85.7)	12.0 (26.1)	<0.0001
Oocyte donation. n (%)	1.0 (1.1)	20.0 (43.5)	<0.0001
IVF. n (%)	12.0 (13.2)	32.0 (70.0)	<0.0001
CHTN. n (%)	6.0 (6.5)	14.0 (30.4)	<0.0001
GDM/DM. n (%)	10.0 (10.9)	12.0 (26.1)	0.03
Post-partum Severe Hypertensive disease			
Severe HTN (%)	17.0 (18.5%)	20.0 (43.5%)	0.004
Proteinuria (%)	0 (0%)	0 (0%)	
Elevated liver enzymes (%)	10.0 (10.9%)	2.0 (4.3%)	NS
Low platelets (%)	6.0 (6.5%)	0 (0%)	NS
Elevated Creatinine (%)	4.0 (4.3%)	7.0 (15.2%)	0.042
Symptoms (%)	11.0 (12%)	3.0 (6.5%)	NS
Headache (%)	5.0 (5.4%)	1.0 (2.2%)	NS
Blurred vision (%)	5.0 (5.4%)	1.0 (2.2%)	NS
Epigastric pain (%)	4.0 (4.3%)	0 (0%)	NS

Data represented as Number (%) or Mean ± SD

BMI-Body mass index. IVF-In vitro fertilization. HTN – Hypertension. CHTN-Chronic hypertension. GDM-Gestational diabetes mellitus. DM- Diabetes mellitus. AMA-Advanced maternal age. YMA-Young maternal age

*Maternal characteristics including demographics, mode of conception, background diseases and Post-partum severe hypertensive disease among AMA vs. YMA women

Table 2. **Maternal Morbidity**

Variables	**YMA (n=92)**	**AMA (n=46)**	**P-value**
GA diagnosis (wks.) median. (IQR)	36.0 (33.0-38.0)	35.5 (32.0-37.0)	NS
GA delivery (wks.) median. (IQR)	37.0 (34.2-38.0)	36.0 (34.0-37.0)	NS
Maximal Systolic BP. mean± SD	160.0±17.0	171.0±14.0	<0.0001
Maximal Diastolic BP. mean± SD	101.0±9.0	103.0±9.0	NS
Severe PE. n (%)	64.0 (69.6)	28.0 (60.9)	NS
HELLP .n (%)	15.0 (16.3)	6.0 (13.0)	NS
Eclampsia. n (%)	1.0 (1.1)	0 (0.0)	NS
MgSo4 treatment. n (%)	47.0 (51.1)	25.0 (54.3)	NS
Hospitalization prior to delivery (days). median. (IQR)	2.0 (1.0-5.0)	4 (1.0-10.0)	NS
No.Medications prior to delivery. median. (IQR)	0 (0-1.0)	0 (0-1.0)	NS
Post partum Hospitalization (days) . median. (IQR)	5.0 (3.0-6.0)	6.0 (5.0-8.0)	<0.0001
No.Medications Post partum. median. (IQR)	0 (0-1.0)	0.5 (0-2.0)	NS
Post partum composite PE Exacerbation. n (%)	26.0 (28.3)	23.0 (50.0)	0.015

Data represented as Number (%) or Mean ± SD or Median + Interquartile range

GA-Gestational age. BP-Blood pressure. HELLP-Hemolysis, Elevated Liver enzymes, and Low Platelet count.PE-Preeclampsia. AMA-Advanced maternal age. YMA-Young maternal age

*Maternal morbidity including characteristics of PE and severe PE, hospitalization and medications pre/post-partum and post-partum complications.

Table 3. **Newborn Characteristics**

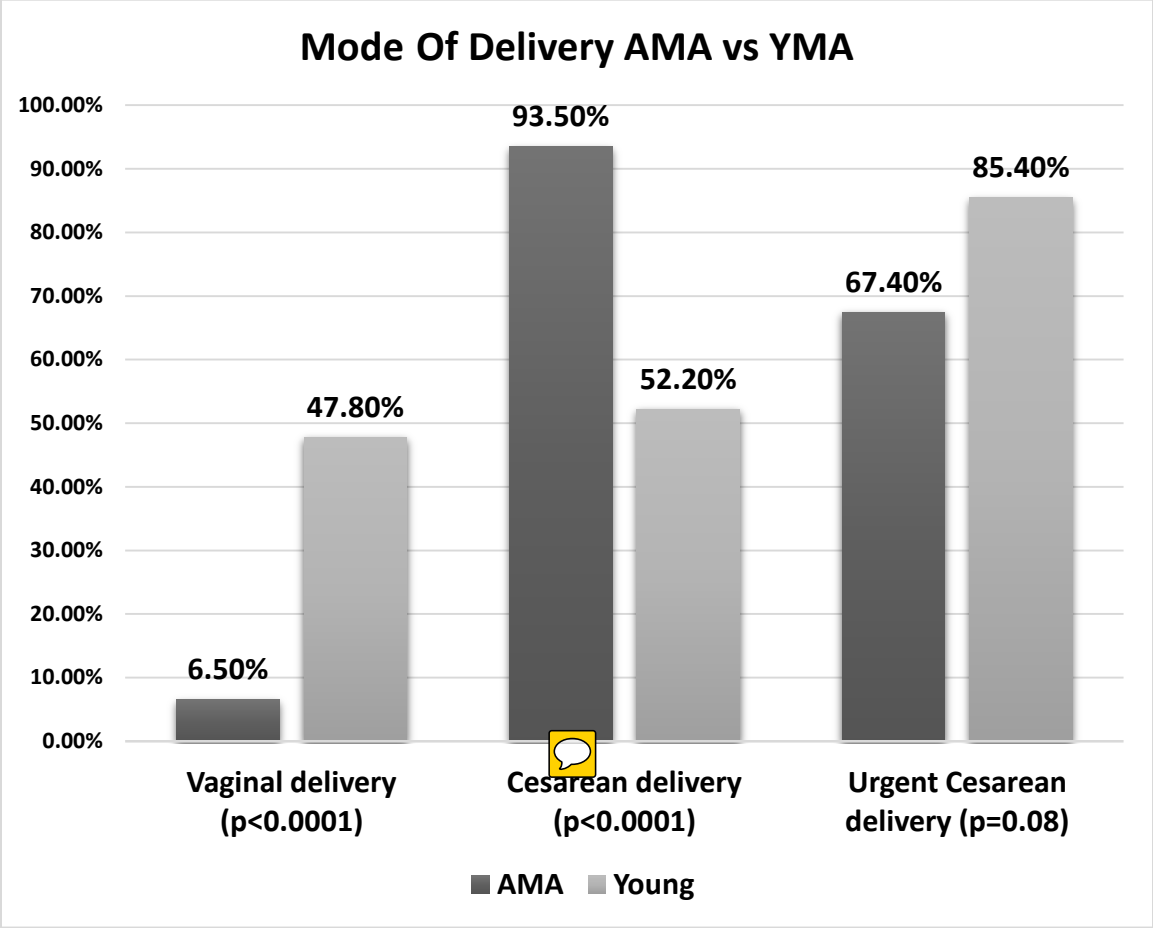
Variables	**YMA (n=92)**	**AMA (n=46)**	**P-value**
gender (male). n (%)	45.0 (48.9)	22.0 (47.8)	NS
Birthweight (g) mean± SD	2495.0±884.0	2336.0±764.0	NS
Cord PH. mean± SD	7.2±0.0	7.2±0.1	NS
SGA. n (%)	22.0 (23.9)	9.0 (19.6)	NS
APGAR 5 min <7. n (%)	1.0 (1.1)	2.0 (4.3)	NS
NICU. n (%)	25.0 (27.2)	15.0 (32.6)	NS
Respiratory disease. n (%)	16.0 (17.4)	10.0 (21.7)	NS
Hypotension. n (%)	4.0 (4.3)	1.0 (2.2)	NS
IVH. n (%)	2.0 (2.2)	0	NS
Severe IVH. n (%)	1.0 (1.1)	0	NS
Death. n (%)	0	0	NS
Composite neonatal morbidity. n (%)	16.0 (17.4)	10.0 (21.7)	NS
Hospitalization (days). median. (IQR)	5.5 (3.0-16.0)	7.0 (5.0-20.0)	NS

Data represented as Number (%) or Mean ± SD or Median + Interquartile range

SGA-Small for gestational age. NICU-Neonatal intensive care unit. IVH-Intra-ventricular hemorrhage. AMA-Advanced maternal age. YMA-Young maternal age

*Newborn characteristics including demographics, weight, postpartum complications and hospitalization.

Figure 1**. Mode of delivery**



AMA-advanced maternal age. YMA-young maternal age.

*Mode of delivery among AMA vs. YMA gravidas including division of caesarean section into urgent and elective operations