**Characteristics and severity of preeclampsia in young and elderly gravidas with hypertensive disease**

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

**Materials & Methods:** A retrospective, small case control study of women diagnosed with preeclampsia in a single tertiary care center. 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**: The rate of severe preeclampsia (60.9 vs 69.6% respectively), HELLP, eclampsia or the need for magnesium treatment did not differ between the groups. However, the AMA group had an increased rate of postpartum presentation or exacerbation of preeclampsia compared to the control group (50.0 vs. 28.3% respectively, p=0.01). In the AMA group, 93.5% of births were by cesarean section (CS) compared to 52.2% in the control group (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 an advanced maternal age carries a similar rate of severe preeclampsia and complications as in young women. However, women over 40 years old have an increased risk for presentation or exacerbation of preeclampsia in the postpartum period and an 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 bearing to fulfill their social, economic and professional aspirations.3,5-8

The mean maternal age of first born children in Israel increased over recent decades from 25 in 1994 to 27.5 in 2015. Over the past 5 years, there was an 8% increase in deliveries among women aged 40 to 44, and a 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 (SGA) and preterm birth.10-21 AMA is additionally associated with higher rates of operative deliveries and cesarean sections (CS).20, 22-25

The risk for preeclampsia increases at advanced maternal age. Women aged 40 or older have a twofold higher rate of preeclampsia compared to the general population.26 Furthermore, oocyte donation commonly used for AMA is associated with as high as 25% risk of preeclampsia.27-30

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

Preeclampsia with severe features may lead to intrauterine growth restriction as well as iatrogenic preterm labor. Hence the fetus is exposed to complications of prematurity, associated with severe morbidity, handicap and even perinatal death.31-32 Exacerbation of the disease during pregnancy or in the immediate postpartum 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.33 Moreover, preeclampsia foretells increased risk for cardiovascular and metabolic disease later in life. 34 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, as well as the timing of the disease, in AMA women compared to a younger population diagnosed with preeclampsia.

**Materials and methods**

A retrospective, small case control study of AMA nulliparous women, who gave birth at one tertiary medical center, between January 1, 2011, and March 30, 2016, and were diagnosed with preeclampsia either prepartum, during labor, or in the immediate postpartum period.

Women at advanced maternal age ≥40 years old (AMA) were compared at a 1:2 ratio to young nulliparous women ≤ 35 years old (young). Inclusion criteria included women with nulliparity, singleton and non-anomalous pregnancies who delivered at ≥24 weeks of gestation and were 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 following: 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 and 159 and diastolic BP between 90 and 109, proteinuria above 300 mg but less than 5 g per 24 hours or urinary test strip of +1 or +2, without any symptoms. Severe features of preeclampsia included: systolic BP greater than 160 and/or diastolic BP greater than 110 , proteinuria of ≥ 5 g per 24 hr or urinary test strip results of ≥ +3, 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), .

For women diagnosed with chronic hypertensive disease, superimposed preeclampsia 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 increased severity of proteinuria as well as occurrence of one of the severe symptoms defined above. Severe hypertensive disease and presentation or exacerbation of preeclampsia during the postpartum period in our study was defined as deterioration of any parameter of preeclampsia.

In our center, women with postpartum severe hypertension are suspected to have severe preeclampsia even without proteinuria due to a high rate of false positives in urine collection after delivery, and are suspected to have HELLP syndrome when having hypertension with elevated liver enzymes and/or low platelets without waiting for full presentation. Therefore, we chose to relate to exacerbation of hypertensive disease in general and not to severe preeclampsia or HELLP syndrome specifically.

Data were extracted from a computerized patient 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 postpartum morbidity, and mode of delivery. Newborn characteristics included birth weight, cord pH, 5-minute Apgar 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.

A composite adverse neonatal outcome was defined as the presence of one or more of the following: cord pH < 7.1, SGA, low birth weight, 5-minute Apgar score < 7, neonatal intensive care unit (NICU) admission, respiratory disease, hypotension, intraventricular 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. Multivariate logistic regression analysis was performed including parameters with p<0.05 in the univariate analysis to determine which factors were significantly and independently associated with severe hypertensive disease and presentation or exacerbation of preeclampsia during the postpartum period. Such factors were identified as those with significance of p<0.05 in the logistic regression.

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 young maternal age women aged 28.5±3.7 y.o. who were diagnosed with preeclampsia. In the AMA group, 43.5% of patients conceived with oocyte donation compared to 1.1% of patients in the young maternal age group (*p<0.0001*). AMA nulliparous gravidas had higher rates of chronic hypertension (30.4 vs. 6.5%, *p<0.0001*) and gestational/pregestational diabetes (26.1 vs. 10.9%, *p=0.03*) than the control group (Table 1). Prior to delivery, 60.9% of AMA had severe preeclampsia and 39.1% had mild preeclampsia, similar to the young maternal age group (69.6% and 31.4% respectively). However, in the postpartum period, the rate of severe preeclampsia was significantly higher in the AMA group than in the control group (50.0 vs. 28.3% respectively, *p=0.01*)

The gestational age at diagnosis or delivery was similar for AMA and young maternal age women (36.0 vs. 35.5 at diagnosis and 37.0 vs. 36.0 at delivery). AMA women had higher maximal mean systolic blood pressure (171.0±14.0) than younger gravidas (160.0±17.0) (*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 MgSO4 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 a higher rate of severe blood pressure than the controls (43.5 vs. 18.5%, *p = 0.004*) and a higher rate of serum creatinine level greater than 1.1 (15.2 vs. 4.3%, *p = 0.042*) (Table 1). Moreover, the AMA group required longer postpartum hospitalization (6.0 ± 2.2 vs. 5.0 ± 4.1 days, *p<0.0001*) (Table 2).

Multivariate logistic regression to predict risk factors for postpartum hypertensive disease was applied to all parameters with a statistical difference of p<0.1 between groups. These included 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 postpartum hypertensive disease: AMA (OR-3.62, CI 1.56-8.38, *p=0.003*), prepartum in-hospital conservative management for preeclampsia (OR-4.51, CI 1.67-12.17, *p=0.003*) and prepartum HELLP syndrome (OR-3.46, CI 1.19-10.06, *p=0.022*).

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

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

**Discussion**

This is the first investigation of the characteristics and severity of preeclampsia among young and elderly gravidas before or after delivery. Our study revealed that advanced maternal age (AMA) women diagnosed with preeclampsia during pregnancy had more severe hypertensive disease in the postpartum period, elevated rate of severe hypertension following delivery, increased rate of serum creatinine level above 1.1 mg/dL and longer hospitalization compared to younger women.

Multivariate analysis revealed that in AMA women, prepartum in-hospital conservative management and prepartum HELLP syndrome were found to be risk factors for postpartum 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 severe HELLP syndrome, eclampsia or a greater need for magnesium treatment during pregnancy.

The association between AMA and severe postpartum preeclampsia has not been 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 women40-42. Cesarean sections may be associated with two factors that can contribute to the higher rate of postpartum preeclampsia observed in the AMA group:
   1. A large volume of fluids was administered during cesarean sections. In some women, delayed or acute mobilization of a large volume of fluid into the intravascular space, particularly in women with suboptimal renal function, can lead to volume overload resulting in hypertension. 35-36.
   2. Nonsteroidal anti-inflammatory drugs (NSAID) are administered for pain management at the Sheba Medical Center following cesarean sections. NSAIDs such as Ibuprofen are associated with vasoconstriction and sodium and water retention, both of which can result in severe hypertension. 38
2. AMA women had a much higher rate of chronic hypertension and superimposed preeclampsia compared to young women (30.4 vs 6.5% respectively in our study). In a study by Peterson et al 37 women with chronic hypertension had an increased need for postpartum antihypertensive medication.
3. New onset postpartum preeclampsia. Vilchez et al 39 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.

In our study, AMA women had an almost twofold higher rate of cesarean sections compared to younger mothers. This result is consistent with other studies that have shown higher rates of cesarean sections among older nulliparous gravidas 40-42. Urgent cesarean sections appeared to be more frequent in the young maternal age group than in the study group (85.4 vs. 67.4%); however, this result was not statistically significant. The most reasonable explanation is that many of the older mothers delivered by elective cesarean section without trial of labor, hence, there were less urgent operations in this group. Other studies have shown conflicting data regarding urgent and elective cesarean sections. Rendtorff et al 40 suggested that there is no difference in urgent and elective cesareans in younger compared to older women, whereas Oakley et al 42 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 or composite neonatal morbidity. This is not suprising, given the lack of difference between the groups in gestational age at delivery and severe features of preeclampsia.

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

Other studies that compared AMA women to a younger population found a higher rate of preeclampsia among women with AMA26. We evaluated for the first time two groups of women that all had preeclampsia, in order to evaluate the severity and characteristics of the disease in each group. 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 increased prevalence of chronic hypertension and most of these women had superimposed preeclampsia, compared to new onset preeclampsia in the young maternal age group. This may be a major contributor to different characteristics of the disease. Moreover, the lack of difference in severity of preeclampsia 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 decision making in regard to mode and timing of delivery. As expected, most AMA women had cesarean sections, however their age did not influence the timing of delivery.

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

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Table 1**. Maternal Characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Units** | **Young (n=92)** | **Advanced (n=46)** | **P-value** |
| Age (y) | mean±SD | 28.5±3.7 | 43.7±3.4 | <0.0001 |
| BMI (kg/m2) | 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 |
| Chronic hypertension | n (%) | 6.0 (6.5) | 14.0 (30.4) | <0.0001 |
| Gestational diabetes mellitus / Diabetes mellitus | n (%) | 10.0 (10.9) | 12.0 (26.1) | 0.03 |
| Postpartum severe hypertensive disease |  |  |  |  |
| Severe HTN | n (%) | 17.0 (18.5) | 20.0 (43.5) | 0.004 |
| Proteinuria | n (%) | 0 (0) | 0 (0) |  |
| Elevated liver enzymes | n (%) | 10.0 (10.9) | 2.0 (4.3) | NS |
| Low platelets | n (%) | 6.0 (6.5) | 0 (0) | NS |
| Elevated creatinine | n (%) | 4.0 (4.3) | 7.0 (15.2) | 0.042 |
| Symptoms | n (%) | 11.0 (12) | 3.0 (6.5) | NS |
| Headache | n (%) | 5.0 (5.4) | 1.0 (2.2) | NS |
| Blurred vision | n (%) | 5.0 (5.4) | 1.0 (2.2) | NS |
| Epigastric pain | n (%) | 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.

\*Maternal characteristics including demographics, mode of conception, background diseases and postpartum severe hypertensive disease among AMA vs. young maternal age women

Table 2. **Maternal morbidity**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Units** | **Young (n=92)** | **Advanced (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 |
| Number of medications prior to delivery | median (IQR) | 0 (0-1.0) | 0 (0-1.0) | NS |
| Postpartum hospitalization (days) | median (IQR) | 5.0 (3.0-6.0) | 6.0 (5.0-8.0) | <0.0001 |
| Number of medications postpartum | median (IQR) | 0 (0-1.0) | 0.5 (0-2.0) | NS |
| Postpartum 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](https://en.wikipedia.org/wiki/Hemolysis" \o "Hemolysis), elevated [liver enzymes](https://en.wikipedia.org/wiki/Liver_enzyme" \o "Liver enzyme), and [low platelet count](https://en.wikipedia.org/wiki/Thrombocytopenia" \o "Thrombocytopenia). PE-Preeclampsia.

\*Maternal morbidity including characteristics of PE and severe PE, hospitalization and medications pre/postpartum and postpartum complications.

Table 3. **Newborn characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Units** | **Young (n=92)** | **Advanced (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-Intraventricular hemorrhage.

\*Newborn characteristics include demographics, weight, postpartum complications and hospitalization.

Figure 1**. Mode of delivery**

\*Mode of delivery among advanced vs. young maternal age women including division of cesarean sections into urgent and elective operations