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# Combined effects of increasing maternal age and nulliparity on hypertensive disorders of pregnancy and small for gestational age

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ABSTRACT

*Background:* The mean age of women delivering for the first time is increasing, and this combination could lead to an increased risk of perinatal complications.
*Objectives:* The objective was to evaluate the potential combined effects of nulliparity and increasing maternal age on small for gestational age (SGA < 10th percentile) and hypertensive disorders of pregnancy (HDP).
*Study design:* A population-based cohort study was conducted using data routinely collected on all births in 11 hospitals in the Burgundy perinatal network between 2007 and 2016. Pregnant women with singleton deliveries aged 20 years or older were included at delivery and divided into groups according to maternal age (20 to 24-year-old group as a reference). Multivariate logistic regression models, adjusted on smoking, body mass index, chronic high blood pressure and birth date, were performed.
*Results:* A total of 137,791 women were included. Whatever the parity, the risks of SGA and HDP increased with maternal age, but the increase began earlier in nulliparous women. Compared to multiparous women, the risk of SGA in nulliparous women increased with maternal age (aOR = 1.5 95% CI [1.4–1.7] for age 20–24 rising to 2.2 [1.8–2.8] for age 40–49). We found evidence that parity modified the association between maternal age and SGA (test for interaction p < 0.001). The risk of HDP was constantly higher in nulliparous women, whatever the maternal age.
*Conclusion:* The combination of increasing maternal age and nulliparity has a more negative impact on the occurrence of SGA than either risk factor alone.

## 1. Introduction

There are multiple factors that can be considered as influencing women to postpone their first pregnancy. In industrialized countries, the evolution of social conditions has resulted in a distinct rise in the mean age of women at delivery [1,2], and this is further accentuated in Europe as described in the recent Eurosperistat report [3]. To reflect these changes, the definition of advanced maternal age (AMA) has also progressed, passing from ≥35 to ≥40 years [1,4,5]. AMA is recognized as an independent risk factor for obstetric and perinatal adverse outcomes (hypertensive disorders of pregnancy (HDP) and small for gestational age (SGA) infants, among others) [6–9].

Giving birth for the first time is also a known risk factor that increases the incidence of HDP [10–12] and SGA infants [13,14].

HDP remains one of the leading causes of maternal mortality [15] and is associated with a long-term risk of cardiovascular and other diseases (i.e. coronary heart disease, type 2 diabetes, and hypertension) [16]. Likewise, SGA babies comprise around 50% of stillbirths, and live

*Abbreviations:* aOR, adjusted odds ratio; AMA, advanced maternal age; BMI, body mass index; CI, confidence intervals; ICD, International Classification of Diseases; HDP, hypertension disorder of pregnancy; SGA, small for gestational age

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born SGA infants have an increased risk of cerebral palsy, cardiovascular disease, obesity and diabetes in adulthood, and metabolic disease [17,18].

As more and more women are having their first child at a later age [19], the assessment of the combination of nulliparity and increasing maternal age on HDP and SGA has a significant interest and could provide both women and healthcare providers with valuable information about the consequences of having a first child later in life.

Our objective was to evaluate the potential combined effects of increasing maternal age and nulliparity on the occurrence of both SGA and HDP during pregnancy. We hypothesized that the two risk factors, when combined, have a more negative effect on outcomes.

## 2. Materials and methods

### 2.1. Data source

Since 2000, all deliveries and terminations of pregnancies that occur within the Burgundy Perinatal Network at or after 22 completed weeks of gestation and/or with a birthweight > 500 g have been systematically recorded in an anonymous database used to regularly assess medical practices and perinatal health [20,21] within the network (Authorization C.N.I.L - Commission Nationale Informatique et Liberté - n° 455451). The Burgundy Perinatal Network database covers all public [11] and private [2] hospitals in Burgundy, a French region with approximately 1,600,000 inhabitants and 17,000 annual births. Maternal and neonatal medical data are prospectively recorded from the mandatory discharge abstracts for each hospitalized patient (used to determine the activity-based funding of hospitals in France). Twenty additional specific perinatal indicators, 11 for each mother and 9 for each newborn, were also prospectively recorded.

Data were rendered anonymous in each hospital using ANONYMAT Software, as previously described [22], before being sent to the committee in charge of the assessment of the perinatal network's performance. A probabilistic linkage was performed which allowed us to assign each woman to their newborn(s), in order to connect all hospital stays of women between 22 weeks gestation and delivery in the Burgundy region.

Data entry was overseen by the physicians in the medical records department, and our statistician compared the records compiled in our database to the birthing room registry in order to ensure exhaustiveness. Statistical coherence was evaluated, and any discrepancies were reported to the medical team and amended.

### 2.2. Study design and population study

A population-based cohort study was conducted in 11 maternities in Burgundy between January 2007 and December 2016. Over this 10-year period, maternities managed approximately 17,000 births per year. In accordance with French perinatal regionalization, there were approximately 3000 births in level-1-maternities, 11,000 births in level-2-maternities and 3000 births in the single level-3-maternity (university hospital) [23]. These facilities are gathered in the hierarchical Burgundy perinatal network, which was accredited by the regional health authorities in 2000.

In the current study, we restricted the analyses to women aged ≥ 20 years (as very young mothers are known to be at a higher risk of certain adverse outcomes [24–26]), with singleton pregnancies and who did not undergo a termination of pregnancy procedure.

We excluded women who gave birth in two private hospitals (14.5% of pregnant women) because the 20 specific indicators were not collected during the entire study period.

### 2.3. Outcomes

The main outcomes included HDP, defined as gestational hypertension, and pre-eclampsia associated or not with complications such as HELLP syndrome, eclampsia and placental abruption (ICD code O13–O140–O141–O142–O150–O45), and SGA for newborns, defined as < 10th percentile for gestational age and gender [27]. We used the International Classification of Diseases (ICD), Tenth revision.

### 2.4. Exposure

The exposure variables were maternal age and parity. Maternal age was divided into 5 groups [20–24, 25–29, 30–34, 35–39 and 40–49 years old) at the time of delivery, and the 20–24 age group was used as the reference group.

We considered women who had never given birth as nulliparous, and those who had given birth to one child or more as multiparous.

### 2.5. Statistical analysis

Qualitative variables were expressed as percentages, and we used $Chi^2$ or Fisher exact tests for comparing distribution between maternal age groups. To evaluate trends in the percentage of obstetric and neonatal complications with maternal age, we used the Cochran-Armitage test.

Multivariate logistic regression models were used to analyze the combined effect of increasing maternal age and nulliparity on the study outcomes, taking into account clinical and healthcare factors known to affect outcomes and our exposure variables. Firstly, we estimated the effect of maternal age according to parity on outcomes. The interaction between maternal age and parity was tested, and we considered that a p-value < 0.05 provided evidence of a possible interaction. Then, we estimated the effect of parity in each maternal age group on outcomes. The adjusted odds ratio (aOR) and their confidence intervals (CI) were reported in both cases.

The variables identified as potential confounders for gestational hypertension and pre-eclampsia outcomes were maternal age, parity, year of birth, body mass index (BMI, $kg/m^2$), and smoking status defined by tobacco consumption in the third trimester. For SGA, it was the same confounders and we added chronic high blood pressure (ICD code O109).

Most variables used in this study had an exhaustiveness of 100% or a low proportion of missing data: less than 5% for maternal age, gestational age, sex, parity and multiple pregnancies. However, BMI data were missing in 30% of cases, making it necessary to analyze complete cases and impute data sets. We used multiple imputation chained equations using the SAS "MI" procedure to impute missing data [28]. Imputation model variables included BMI, gestational age, caesarean delivery, HDP, gestational diabetes, instrumental delivery, major postpartum hemorrhage, parity, maternal age, birth date, chronic high blood presure and smoking. We generated 30 independent imputed datasets, and estimates were pooled according to Rubin's rule [29]. To test the robustness our result, we conducted several sensitivity analyses.

Statistical analyses were performed using SAS software 9.3 (SAS Institute, Cary, NY, USA). The differences were considered significant at $p < 0.05$ (2-tailed).

## 3. Results

### 3.1. Study population

In total, 144,312 women delivered in the 11 public maternities of the Burgundy Perinatal Network over the study period. Overall, 137,268 singleton births from women aged between 20 and 49 years were included in the study. The study flow chart is presented in Supplementary Fig. 1.

Maternal characteristics are presented in Table 1. The proportion of nulliparous women decreased as maternal age increased, amounting to 19.7% in the oldest age group.

**Table 1**
Maternal characteristics according to maternal age.

| | Maternal age groups (years) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20–24 | | 25–29 | | 30–34 | | 35–39 | | 40–49 | | Total | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| | 23,084 | 16.8 | 49,113 | 35.8 | 41,436 | 30.2 | 19,083 | 13.9 | 4552 | 3.3 | 137,268 | 100.0 |
| Parity | | | | | | | | | | | | |
| Nulliparous | 14,673 | 66.3 | 23,855 | 50.8 | 12,197 | 31.0 | 3916 | 21.9 | 823 | 19.7 | 55,464 | 42.5 |
| Multiparous | 7453 | 33.7 | 23,131 | 49.2 | 27,179 | 69.0 | 13,955 | 78.1 | 3357 | 80.3 | 75,075 | 57.5 |
| *Missing values* | *958* | | *2127* | | *2060* | | *1212* | | *372* | | *6729* | |
| Body Mass Index | | | | | | | | | | | | |
| < 18.5 | 1734 | 10.8 | 2611 | 7.5 | 1955 | 6.7 | 814 | 6.0 | 174 | 5.5 | 7288 | 7.5 |
| [18.5–25[ | 9312 | 57.9 | 20,863 | 60.2 | 17,714 | 60.7 | 7752 | 57.5 | 1700 | 53.3 | 57,341 | 59.4 |
| [25–30[ | 3062 | 19.0 | 6987 | 20.1 | 5802 | 19.9 | 2903 | 21.6 | 776 | 24.3 | 19,530 | 20.2 |
| ≥30 | 1987 | 12.3 | 4221 | 12.2 | 3711 | 12.7 | 2003 | 14.9 | 539 | 16.9 | 12,461 | 12.9 |
| *Missing values* | *6989* | | *14,431* | | *12,254* | | *5611* | | *1363* | | *40,648* | |
| Assisted Reproductive Technology* | 63 | 0.3 | 482 | 1.0 | 758 | 1.8 | 485 | 2.5 | 142 | 3.1 | 1930 | 1.4 |
| Nulliparous** | 54 | 0.4 | 386 | 1.6 | 493 | 4.0 | 265 | 6.8 | 82 | 6.4 | 1280 | 2.3 |
| Multiparous*** | 8 | 0.1 | 84 | 0.4 | 238 | 0.9 | 199 | 1.4 | 54 | 1.6 | 583 | 0.8 |
| *Missing values* | *1* | | *12* | | *27* | | *21* | | *6* | | *67* | |
| Smoking | 4118 | 17.8 | 5746 | 11.7 | 4340 | 10.5 | 2095 | 11.0 | 535 | 11.7 | 16,834 | 12.3 |
| Chronic high blood pressure | 6 | 0.03 | 53 | 0.1 | 72 | 0.2 | 69 | 0.4 | 38 | 0.8 | 238 | 0.2 |

* Assisted Reproductive Technology is defined as women who have recourse to assisted reproduction.
** Percentage of Assisted Reproductive Technology for nulliparous women.
*** Percentage of Assisted Reproductive Technology for multiparous women.

### 3.2. Hypertensive disorders of pregnancy according to both maternal age and parity

Whatever the parity, the prevalence of gestational hypertension and pre-eclampsia increased with maternal age (test for trend $p < 0.05$) (Supplementary Table 1). In the results of the adjusted logistic regression analysis, we observed an increased risk for gestational hypertension and pre-eclampsia with maternal age in both nulliparous and multiparous women. However, the increased risk began earlier, from age 25–29, in nulliparous women.

The combination of increasing maternal age and nulliparity did not have a more negative effect on HDP outcomes (the interaction test was non-significant) (Table 2).

Compared to multiparous women, nulliparous women were at higher odds of HDP in all age groups (Table 3).

### 3.3. Small for gestational age infants according to both maternal age and parity

We observed an increased risk for SGA (< 10th) with maternal age from age 30–34, in nulliparous women (Table 2). As maternal age increased, the risk of SGA (< 10th) rose faster in the nulliparous 40–49 year old groups (nulliparous aOR = 1.7 [1.4–2.1], multiparous aOR = 1.3 [1.1–1.5]; test for interaction p-value < 0.001).

Whatever the maternal age, nulliparous patients have a higher risk of SGA (< 10th percentile) than multiparous women. The risk rose

**Table 2**
Adjusted Odds Ratios for primary outcomes according to increasing maternal age and parity after multiple imputation.

| | Maternal age groups (years) | | | | | |
|---|---|---|---|---|---|---|
| | 20–24 OR | 25–29 aOR [CI 95%] | 30–34 aOR [CI 95%] | 35–39 aOR [CI 95%] | 40–49 aOR [CI 95%] | p-value for interaction§ between maternal age and parity |
| Gestational hypertension | | | | | | |
| Nulliparous | 1 | 1.3** [1.1; 1.4] | 1.4** [1.2; 1.7] | 1.8** [1.4; 2.2] | 2.9** [2.1; 4.1] | NS |
| Multiparous | 1 | 1.2 [0.9; 1.5] | 1.2 [0.9; 1.6] | 1.8** [1.4; 2.4] | 2.7** [1.9; 3.7] | |
| Pre-eclampsia | | | | | | |
| Nulliparous | 1 | 1.3* [1.1; 1.5] | 1.4** [1.2; 1.7] | 1.6** [1.3; 2.1] | 2.1** [1.3; 2.3] | NS |
| Multiparous | 1 | 1.1 [0.8; 1.5] | 1.1 [0.8; 1.5] | 1.6* [1.2; 2.2] | 2.2** [1.5; 3.2] | |
| SGA | | | | | | |
| Nulliparous | 1 | 0.9 [0.9; 1.0] | 1.1** [1.1; 1.2] | 1.4** [1.3; 1.6] | 1.7** [1.4; 2.1] | < 0.001 |
| Multiparous | 1 | 0.9 [0.8; 1.0] | 1.0 [0.9; 1.1] | 1.1 [1.0; 1.2] | 1.3** [1.1; 1.5] | |

CI: Confidence Interval. aOR: adjusted Odds Ratio. SGA: Small for gestational age < 10th percentile. NS: Non Significant. *p < 0.05. **p < 0.001.
§: Interaction between maternal age and parity.
For Gestational Hypertension and Pre-eclampsia, our models were adjusted for year of birth, Body Mass Index (BMI) and smoking.
For Small for gestational age outcomes, our model was adjusted for year of birth, BMI, smoking and chronic high blood pressure.

**Table 3**
Comparison of nulliparous to multiparous women for primary outcomes according to maternal age after multiple imputation (2007 – 2016).

| | Maternal age groups (years) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 20–24 | | 25–29 | | 30–34 | | 35–39 | | 40–49 | |
| | *Ref* OR | Nulliparous aOR [CI 95%] | *Ref* OR | Nulliparous aOR [CI 95%] | *Ref* OR | Nulliparous aOR [CI 95%] | *Ref* OR | Nulliparous aOR [CI 95%] | *Ref* OR | Nulliparous aOR [CI 95%] |
| HDP | | | | | | | | | | |
| Gestational hypertension | 1 | 2.0** [1.5; 2.6] | 1 | 2.1** [1.8; 2.5] | 1 | 2.3** [2.0; 2.8] | 1 | 1.9** [1.5; 2.4] | 1 | 2.1** [1.4; 3.0] |
| Pre-eclampsia | 1 | 1.8** [1.3; 2.4] | 1 | 2.0** [1.7; 2.4] | 1 | 2.3** [1.9; 2.7] | 1 | 1.8** [1.4; 2.3] | 1 | 1.6 [1.0; 2.7] |
| SGA | | | | | | | | | | |
| < 10th percentile | 1 | 1.5** [1.4; 1.7] | 1 | 1.7** [1.5; 1.8] | 1 | 1.9** [1.8; 2.1] | 1 | 2.2** [1.9; 2.4] | 1 | 2.2** [1.8; 2.8] |

*Ref*: multiparous women. CI: Confidence Interval. aOR: adjusted Odds Ratio. HDP: Hypertension Disorders of Pregnancy. SGA: Small for Gestational Age. **p < 0.001. For Gestational Hypertension and Pre-eclampsia, our models were adjusted for year of birth, Body Mass Index (BMI) and smoking. For Small for gestational age outcomes, our model was adjusted for year of birth, BMI, smoking and chronic high blood pressure.

along with maternal age, with aOR = 1.5 95% CI [1.4–1.7] for age 20–24 rising to 2.2 [1.8–2.8] for age 40–49 (Table 3).

The results of sensitivity analyses were similar (Supplementary Table 2).

## 4. Discussion

### 4.1. Principal findings

Our findings highlight that, whatever the parity, the risks of gestational hypertension, pre-eclampsia and SGA infants increased with maternal age. These increases began earlier in nulliparous women, from 25 to 29 years onwards for HDP outcomes and from 30 to 34 years onwards for SGA. We also found that nulliparous women were more at risk of HDP and SGA than multiparous women.

The combination of nulliparity and increasing maternal age have a more negative effect on SGA, since the risks of SGA were similar for younger women regardless of parity, but for older women, nulliparity resulted in a higher risk of SGA.

### 4.2. Strengths and limitations of this study

The strengths of our study include the fact that it is a large, prospectively collected regional cohort which provided 10 years of reliable data. The characteristics of our population were comparable to the 2016 French National Perinatal Surveys [30], which reported an equivalent proportion of both women aged 40 years or older (4.0%) and nulliparous women (42.2%). Private hospitals were excluded, which limits the generalization of our results.

Previous studies have investigated the combined effects of parity and maternal age on HDP and SGA [31–33], but they were mainly focused on advanced maternal age with thresholds defined at ≥35 or ≥40 years. Few studies did not use a maternal age threshold [12,34–37]. They found an association between obstetric and neonatal outcomes and increasing maternal age. Only one study stratified by parity [12], but no comparison was made because the objective of this paper was to describe the incidence of pregnancy associated with HDP according to parity and ethnicity. In the other studies, parity was used as an adjustment factor or selection criteria, meaning that the combined effect of parity and maternal age was not investigated.

This paper found evidence that, whatever the maternal age group, nulliparity has an independent effect. The association of this risk factor with increasing maternal age led to an earlier increased risk of HDP and SGA. We also found a significant effect of combined maternal age and parity on the risk of SGA, revealing that these two risk factors have a strong negative effect when combined.

The weaknesses of this study include the limited number of mothers with AMA and unmeasured potential confounders such as ethnicity and social deprivation. However, our population comes from a large and homogenous Caucasian multicentric database of births managed in a hierarchical perinatal network, and the French health care system provides every pregnant woman with free access to medical care during pregnancy.

Another limitation was the amount of missing data. To mitigate this, we used multiple imputation to account for missing data, and we performed sensitivity analyses to test the robustness of our results.

Given the reliance on ICD-10 codes for the ascertainment of outcomes, there was a potential for under-detection-related bias [38]. Nevertheless, coding quality is checked in a standardized manner in each hospital by medical information professionals to correct diagnoses and improve the recording of comorbidities (internal quality assessment), and, each year, our assessment unit carried out quality checks with medical information professionals.

HDP and fetal growth disorders share a common placental origin and can be defined as placental vascular disorders [39,40]. Given the design of our study, we were not able to identify fetal growth restriction, but we used growth curves adjusted for gestational age and gender [27].

### 4.3. Study findings in context

More and more women postpone childbirth, and the proportion of nulliparous women represents up to 20% in the oldest age group. To cope with this situation, women of childbearing age should be made aware of the obstetric and perinatal risks of delayed pregnancy, in particular in women undergoing assisted reproductive technology, with or without oocyte vitrification, who tend to be nulliparous and older.

These findings may have significant implications in clinical practices. The association of these two factors could constitute major criteria for increased monitoring during pregnancy.

## 5. Conclusions

Whatever the parity, the risks of HDP and SGA increase with maternal age, but the increase appears earlier in nulliparous women. As maternal age increases, the risk of SGA rises faster in nulliparous women than in multiparous women. These results are all the more important that the proportion of older nulliparous women will likely continue to grow over the coming decades.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Authors' contributions

T Desplanches was involved in study design, analysis and interpretation of the results and drafted the initial manuscript and revised the manuscript. E Szczepanski and J Cottenet were involved in analysis and interpretation of data, and reviewed the manuscript. P Fauque, C Quantin and P Sagot were involved in study design, analysis, and interpretation of data, and reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.09.006.

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