



Comparison of risk factors and perinatal outcomes in early onset and late onset preeclampsia: A cohort based study in Reunion Island



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ABSTRACT

Clinical differences, maternal risk factors and pregnancy outcomes of deliveries complicated by early- (delivery < 34 weeks) and late-onset (delivery ≥ 34 weeks) preeclampsia were studied in a cohort of women in Reunion Island during 15 years (period 2001–2015; N = 62,230 pregnancies). The overall preeclampsia rate in singleton pregnancies was 2.37%. Early- and late-onset preeclampsia rates were 0.75% and 1.5% respectively, and the trend for each type of disease was stable over time. In both form of preeclampsia, smoking during pregnancy was a protective factor and associated risk factors were: older age, primiparity, pre-existing diabetes, chronic hypertension, higher pre-pregnancy body mass index and obesity, infertility treatment, history of renal disease and hypercholesterolemia (all $p < 0.05$). The rate of caesarean section, medically-induced delivery and impaired foetal and neonatal outcomes were significantly higher in preeclamptic women (all $p < 0.0001$). When comparing early- versus late-onset preeclampsia, the only difference was the older maternal age in primiparae with early-onset preeclampsia ($p = 0.02$), and the two groups of preeclamptic women were similar in terms of maternal risk factors, with the exception of higher rates of chronic hypertension in early-onset preeclampsia ($p = 0.02$). Foetal and neonatal outcomes were evaluated after adjustment for gestational age at delivery and no difference was detected between early- and late-onset preeclamptic women. These analyses failed to identify a specific phenotype of preeclampsia in terms of predisposition or pre-existing risk factors for one form or another. Gestational age at delivery was the most important predictor for offspring outcome.

1. Introduction

¹It is well recognized that preeclampsia is a heterogeneous syndrome and that the clinical characteristics of the early-onset preeclampsia (EO-PE, gestational age at delivery < 34 weeks) and late-onset disease (LO-PE, ≥ 34 weeks) are different (Sibai et al., 2005). The pathophysiology of the two disorders is also supposed to be different: Vatten et al. have suggested that preterm delivered preeclampsia associated with low birthweight may be caused by underlying placental abnormality, whereas pre-eclampsia delivered at term may represent a mixture of conditions, ranging from mild pre-eclampsia with moderate placental affection to hypertensive conditions in pregnancies without placental dysfunction. (Vatten and Skjaerven, 2004). Recently, Redman et al. have suggested that the LO-PE form also relies on the placenta, but that the placenta perfusion problems at term are due to a different placenta problem than the dysfunctional spiral artery remodelling

pathway, which is more typical of the EO-PE pathophysiology (Redman et al., 2014; Redman and Staff, 2015).

Several publications have described the associated maternal morbidities, birth outcomes, clinical and laboratory features of the two preeclampsia types (Ny and Cheng, 2016; Kucukgoz Gulec et al., 2013; Lisonkova and Joseph, 2013). The mother's younger age at first birth (Robillard et al., 2007) and some maternal risk factors (such as metabolic syndrome and hypertension) have been addressed for having important roles in development of the EO- and the LO-form, respectively. Also, maternal, foetal and neonatal complications are different in EO-PE compared to LO-PE (Aksornphusitaphong and Phupong, 2013; Lisonkova et al., 2014).

In general, within a population, both forms are represented, with the vast majority of women developing LO-PE (and so, mild neonatal signs) and a minority presenting EO-PE (and so, prematurity and impaired perinatal outcome) (Chaiworapongsa et al., 2014). However, we

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¹ Abbreviations: BMI (body mass index), EO-PE (early-onset preeclampsia); IVF (in vitro fertilization), ICSI (intra-cytoplasmic sperm injection); IUFD (intrauterine foetal death); LO-PE (late-onset preeclampsia); MTP (medical termination of pregnancy); SGA (small for gestational age).

recently showed that predominance of early- or late-onset preeclampsia may have huge geographical differences as the rate of EO-PE (defined as preeclampsia delivered before 34 weeks of gestation) was strikingly high (31.2% of all preeclampsia) in a cohort from Reunion Island, compared to other countries (8–10%) (Iacobelli et al., 2015).

Reunion Island is a French department in the Southern Indian Ocean. The peculiarity of this tropical region lays in the multiethnic origin of inhabitants [Africa and intermixed population (50%), Europe (27%), India (20%) and China (3%)]. Compared to Europe and mainland France, there is a younger reproductive population (the mean age at primiparity is approximately 23 years). Finally, accessibility to maternity services is easy, and high-quality care is provided free of charge by the French healthcare system.

The aim of the present study was to compare the clinical differences, the maternal risk factors and the pregnancy outcomes between EO-PE and LO-PE in this particular population of preeclamptic women with a very high prevalence of preterm delivery.

2. Materials and methods

2.1. Design and study population

“Southern Reunion” identifies a specific geographic and health area of our department, with 5400 deliveries on average per year, occurring in three facilities (2 primary care and 1 tertiary care center). In this territory, all preeclampsia are referred to the tertiary care maternity of Saint Pierre University hospital.

This was an observational cohort study of all singleton preeclamptic pregnancies who delivered in this third level center over 15 years (January 2001 to December 2015).

2.2. Clinical data and variables

The study sample was drawn from the hospital perinatal database, which prospectively records data of all mother-infant pairs since 2001. Information is collected at the time of delivery and at the time of infant hospital discharge and regularly audited by appropriately trained staff; for the purpose of this study, records have been validated and have been used anonymously. Maternal characteristics and clinical risk factors examined for potential association with preeclampsia included: maternal age, parity and gravidity, marital status, education, smoking or alcohol assumption during pregnancy, infertility treatment, pre-pregnancy body mass index (BMI), diabetes mellitus, chronic hypertension prior to pregnancy, coagulopathy, hypercholesterolemia, history of preeclampsia, history of renal or thyroid disease and congenital malformation. The following delivery and pregnancy outcomes were analyzed: medically induced delivery, caesarean section, abnormal foetal heart rate, postpartum haemorrhage, intrauterine foetal death [(IUFD) *in utero* or *intrapartum* death of a foetus delivered at 22 weeks of gestation or later], medical termination of pregnancy (MTP), early neonatal death (death between 1 and 7 days of life) and perinatal death (defined as IUFD + MTP + early neonatal death), HELLP syndrome, and eclampsia. The neonatal outcomes of interest were: gestational age at birth, birth weight, sex, Apgar@1 min \leq 3, small for gestational age, (SGA, according to Brenner et al., 1976) and need for intubation at birth.

2.3. Definition of exposure

Preeclampsia was defined according to the international recommendations which were used during most of the period covered in this study: systolic blood pressure \geq 140 mmHg or \geq diastolic 90 mmHg at bed rest on at least two occasions 6 h apart, and proteinuria (excretion of \geq 0.3 g/day, or at least 1+ on a urine reagent strip), measured after the 20th week of pregnancy (No authors listed, 2000).

Preeclampsia outcome was categorized in two groups: EO-PE and

LO-PE defined as delivery before 34.0 and \geq 34.0 weeks, respectively.

2.4. Statistical analysis

Categorical variables were presented as frequencies and continuous variables as means \pm SDs.

Bivariate comparisons were performed using χ^2 test, or Fisher exact test for qualitative variables and ANOVA or Kruskal-Wallis test when appropriate.

First, women with preeclampsia were compared to women without preeclampsia. Second, EO-PE were compared to LO-PE. In a second stage of analysis, we estimated the effect of dichotomizing gestational age at delivery before 37.0 and \geq at 37 weeks on maternal characteristics and risk factors. Comparative analysis of delivery and neonatal outcomes was adjusted for gestational age at birth when appropriate.

Because at bivariate analysis preeclamptic women had significantly higher rates of pre-pregnancy BMI and BMI $>$ 30 kg/m², and following the previous observation of the impressive increase of obesity in pregnant women at Reunion Island (Robillard, 2014), in a supplementary analysis, we plotted the trend of obesity rate with that of both EO-PE and LO-PE over the study period in the observed population. A *p* value $<$ 0.05 was considered significant.

2.5. Ethics

This study was conducted in accordance with French legislation. As per to the French law a specific approval of an ethics committee is not required for this non-interventional study based on retrospective, anonymized data and written consent is not needed.

3. Results

3.1. Epidemiology of preeclampsia

Over the study period 62,330 deliveries occurred in the maternity department and were recorded in the database. The incidence of preeclampsia in this entire cohort was 2.37%, with rates of 2.29% and 6.85% in singleton and multiple deliveries respectively.

For the purpose of the study, only singleton deliveries (N = 61,062) were analyzed. The total number of preeclampsia over the study period was 1397 and the frequency of EO-PE and LO-PE was respectively 0.75 (464 of 61,062) and 1.5 (933 of 61,062) per 100 deliveries. Among all preeclampsia, 33.21% were EO and 66.79 were LO. Among alive births from preeclamptic delivery, 60% were preterm (born less than 37 weeks of gestation) and 40% were at term (\geq 37 weeks of gestation). Among all infants 413 (31%) were $<$ 34, 386 (29%) were 34–36 and 534 (40%) were \geq 37 weeks of gestation.

3.2. Sociodemographic characteristic of the study population and comparison between EO-PE and LO-PE

Table 1 shows sociodemographic characteristics of the study population. Preeclamptic women were in general older and more often primiparae than no preeclamptic ones. The only difference when comparing EO-PE and LO-PE was the older age of primiparae with EO-PE.

When dichotomizing preeclampsia into preterm and term delivered groups ($<$ 37 and \geq 37 weeks of gestation, respectively) we found statistically significant differences between the groups for marital status and education (lower rates of “single” marital status and lower education level in EO-PE compared to LO-PE, *p* respectively = 0.03 and 0.04, data not shown). Sociodemographic characteristics of preeclamptic women were not different in patients who delivered a SGA infant (data not shown).

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