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Recurrent or first preeclampsia in multiparae: A case-control study of singleton pregnancies in Reunion Island☆

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ABSTRACT

Recurrent or first preeclampsia in multiparae : a case-control study of singleton pregnancies in Reunion Island

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Objective: To compare multiparous women with a first occurrence of preeclampsia and those with recurrent preeclampsia in singleton pregnancies.

Study design: a 17.5-year (2001–2018) case-control study conducted in the University's maternity of South Reunion (Indian Ocean), comparing 125 patients with recurrent preeclampsia and 742 patients with a first episode of the disease (controls). Statistical analyses were performed with use of the Student *t*-test for comparison of continuous data and the Chi-square or Fisher exact test for comparison of categorical variables.

Results: There was no difference between the two groups concerning socio-demographic characteristics, post-partum haemorrhage, perinatal mortality rates. Nevertheless, recurrent preeclamptic women had a higher risk to present with prior chronic hypertension (OR 2.05 [1.30–3.23], p = 0.002), and to experience an early onset preeclampsia (< 34 weeks) compared to controls (OR 1.69 [1.15–2.48], p = 0.007). Women with recurrent preeclampsia were more prone to have C-sections (OR 1.63 [1.06–2.51], p = 0.024) mainly because of maternal indications (89.2% vs 76.4%, p = 0.008). Newborns from recurrent preeclampsia were more likely to have very low birthweight < 1500 g (OR 1.79 [1.16–2.77], p = 0.001), while there was no significant difference for gestational ages (34.1 vs 34.7 weeks).

Conclusion: Recurrent multiparous preeclamptic women presented more severe maternal disease (with a higher rate of early onset preeclampsia). Persistent hypertension in women with a history of preeclampsia is a risk factor for developing recurrent preeclampsia, and these patients should be monitored more closely.

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Introduction

Preeclampsia (PE) is a pregnancy complication characterized typically by hypertension and proteinuria with first onset in the second half of pregnancy. It is a major cause of fetal growth restriction and medically-induced preterm delivery with associated neonatal morbidity and mortality. [1] This disease affects both the offspring and the mother as complications related to preeclampsia are also consistently among the top causes of maternal death in developed and developing countries [2–4] Indeedearly complications of preeclampsia include: HELLP syndromehemolysis elevated liver enzymes, and low platelet count) eclampsia, and placental abruption. Women with previous PE are at increased risk to develop cardiovascular diseases in later life [5,6]. Despite preventive measures to decrease the risk of recurrent PE and maternal sequelae the recurrence rates of PE have not declined over the past 20 years. [7]

Abbreviations: BMI, body mass index; CI, confidence interval; HELLP syndrome, hemolysis, elevated liver enzymes, and low platelet count; OR, odds ratio; PE, preeclampsia; RPE, recurrent preeclampsia; SD, standard deviation.

☆ Study conducted in Reunion Island, France.

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In mainland France, the incidence of PE is estimated between 1 and 3% in the nulliparous and between 0.5 and 1.5% in the multipara women. [8] In Reunion Island, a French overseas department in Indian Ocean, the average incidence of PE is about 2.47%, with rates of 2.3% and 6.6% in singleton and multiple deliveries respectively [9].

Preeclampsia has generally been described as a disease of nulliparas, but a first episode is known to increase the risk of developing the same pathology in subsequent pregnancies [10].

Previous studies comparing first and recurrent PE are contradictory. Chen found that recurrent preeclampsia seemed to be less severe, with a better perinatal outcome than in nulliparas, [10] whereas Cormick stated that recurrent preeclampsia was associated with more severe disease and associated morbidities [11].

Thus, our main objective was to compare obstetrical and neonatal outcomes in multiparous pregnancies with first and recurrent episode of PE, within a nested cohort of women delivering in Southern Reunion Island over a 17.5-year study period.

Material and methods

Setting and study design

Reunion Island is a French overseas department of 850 727 inhabitants, with a surface area of 2500 km^2. Saint-Pierre is the second city of the island with 85 059 inhabitants. [12] All preeclampsia in the southern part of the island (representing approximately 40% of total births of the island) are referred to the tertiary care maternity of Saint Pierre University Hospital, having among 5000 deliveries on average per year. The study design was a case-controlled study including all multiparous women with singleton gestation and preeclampsia, during a 17.5-year period (1st of January 2001 to 30th of June 2018).

Data collection

Data were collected using the software EpiData. Clinical data were drawn from the hospital perinatal database, which prospectively records demographic, gestational and perinatal variables of mother-neonate pairs since 2001. Information was collected at the time of delivery and at the time of neonate/infant hospital discharge. For the purpose of this study, records have been used anonymously. Maternal characteristics included: maternal age and demographic data, ante-natal body mass index (BMI) [weight (kg)/height (m^2)], parity and gravidity, smoking and alcohol assumption during pregnancy, marital status, educational level, socio-professional category, pre-existing clinical and gynecological diseases, pregnancy characteristics including : number of prenatal consultations, time before first echography, weight gain, obstetric

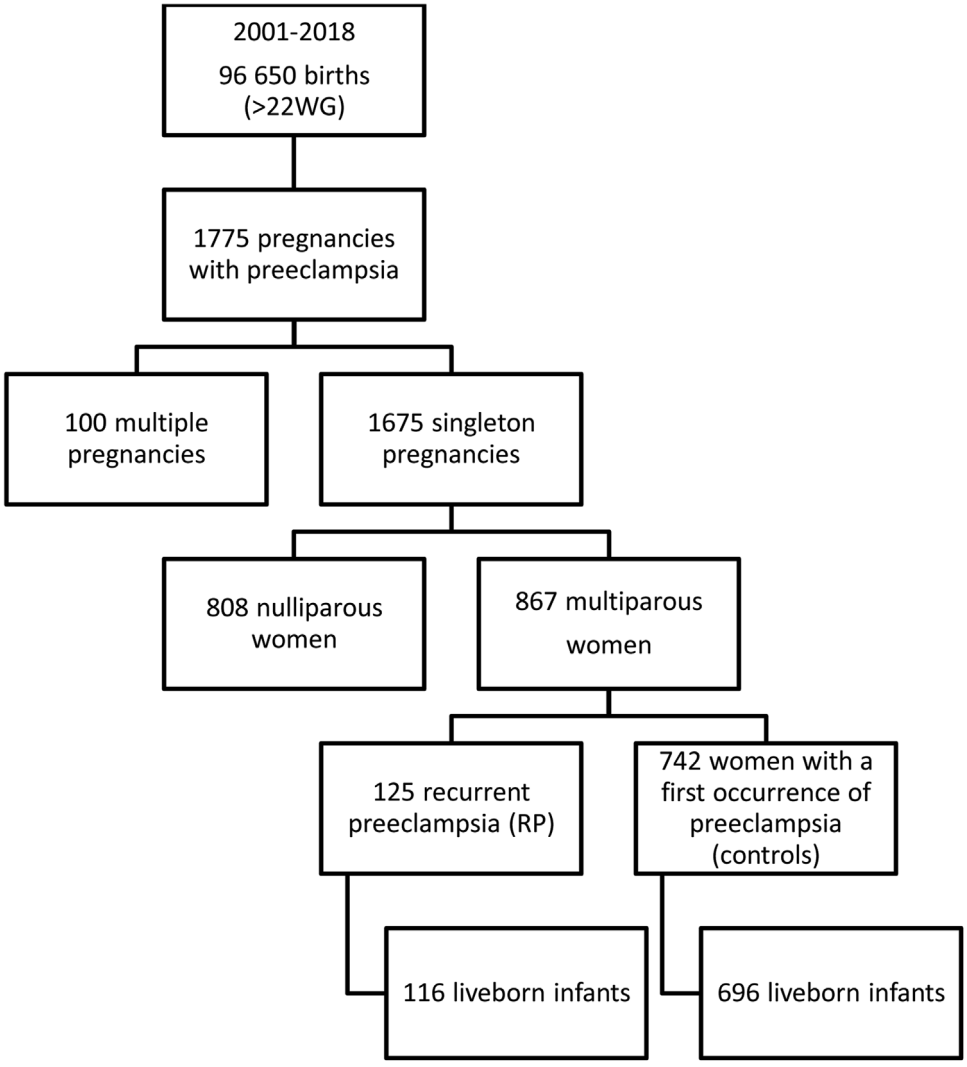

Fig. 1. Flow chart.

WG = weeks of gestation.

Table 1
Maternal characteristics.

Maternal characteristics	Recurrent preeclampsia N = 125 (%)	First occurrence of preeclampsia N = 742 (%)	OR [95% CI]	p-value
Maternal age (SD)	31.61 ± 5.31	32.24 ± 6.14		0.280
Gestity ± sd	4.00 ± 2.02	4.08 ± 2.03		0.700
Parity ± sd	2.33 ± 1.67	2.32 ± 1.64		0.950
Multiparous women (≥5)	23 (18.4)	143 (19.3)	0.94 [0.58-1.54]	0.819
Age ≥ 35 years	39 (31.2)	288 (38.8)	0.71 [0.48-1.07]	0.104
BMI (mean ± sd, kg/m^2)	28.85 ± 7.31	27.95 ± 6.89		0.39
BMI categories				0.201
• ≤19 (underweight)	11 (9.4)	63 (9.3)		
• 20-24 (normal)	30 (25.6)	191 (28.4)		
• 25-29 (overweight)	31 (26.5)	184 (27.4)		
• 30-34 (obesity)	19 (16.2)	132 (19.6)		
• 35-39 (severe obesity)	18 (15.4)	71 (10.6)		
• >40 (morbid obesity)	8 (6.9)	31 (4.5)		
Smoking	13 (10.4)	82 (11.1)	0.93 [0.50-1.73]	0.826
Alcohol	2 (1.6)	5 (0.7)	2.39 [0.46-12.46]	0.286
History of elective abortion	28 (22.4)	138 (18.6)	1.26 [0.80-2.00]	0.318
History of micarriage	30 (24)	185 (24.9)	0.95 [0.61-1.48]	0.823
Marital status :				0.392
• Single	32 (25.6)	197 (26.5)		
• With a partner	57 (45.6)	286 (38.5)		
• Married	34(27.2)	226 (30.5)		
• Divorced/widow	0 (0)	6 (0.8)		
Education level:				0.347
• None	5 (4.0)	16 (2.2)		
• Elementary school	55 (44.3)	373 (50.4)		
• Apprenticeship	6 (4.8)	17 (2.3)		
• High school	27 (21.8)	182 (24.6)		
• University	24 (19.4)	109 (14.7)		
• Unknown	7 (5.6)	43 (5.8)		
Socioprofessional group:				0.641
• Unemployed	71 (72.4)	465 (75.5)		
• Farmer	1 (1.0)	1 (0.2)		
• Craftswoman	1 (1.0)	6 (1.0)		
• Employees	16 (16.4)	97 (15.7)		
• Senior executive	3 (3.1)	6 (1.0)		
• Associate professional	2 (2.0)	10 (1.6)		
• Teacher	1 (1.0)	12 (1.9)		
• Medical/ paramedical	2 (2.0)	17 (2.8)		
• Unknown	1 (1.0)	2 (0.3)		
Origin:				0.541
• Reunion Island	107 (85.6)	618 (83.3)		
• Mayotte	14 (11.2)	68 (9.2)		
• Comores	1 (0.8)	9 (1.2)		
• Madagascar	0 (0)	15 (2.0)		
• Metropolitan France	3 (2.4)	22 (3.0)		
• Mauritius	0 (0)	5 (0.7)		
• Other	0 (0)	5 (0.7)		

history and illnesses (diabetes, hypertension, onset of preeclampsia), labour and delivery complications (post-partum hemorrhage), labor induction, rupture of membranes, mode of delivery (vaginal/caesarean section), intra-uterine fetal death, medical termination of pregnancy. The neonatal outcomes of interest were: gestational age at birth, birth weight, gender, Apgar score, apparition of infant respiratory distress syndrome during the stay in neonatal department, and neonatal death in the first month of life.

Definition of exposure, variables and outcomes

Preeclampsia was defined according to the World Health Organization recommendations [13] and the International Society for the study of Hypertension in Pregnancy [14], as the new onset of hypertension (BP ≥ 140 mmHg systolic or ≥90 mm Hg diastolic) at or after 20 weeks' gestation and substantial proteinuria (> 0.3 g/24 h). Early onset preeclampsia was defined as preeclampsia that developed before 34 weeks of gestation. Multiparous patients were categorized into two groups: women with preeclampsia in a prior pregnancy (cases, RPE) and women with a first occurrence of PE (controls).

Statistical analysis

Categorical variables were presented as frequencies and continuous variables as means ± SDs. Statistical analyses were performed with use of the Student *t*-test for comparison of continuous and normally distributed data and the Chi-square or Fisher exact test for comparison of categorical variables. Odds ratio with 95% confidence interval (OR 95% CI) of maternal and neonatal outcomes in relation to preeclampsia were also calculated. Variables significant at a p-level value < 0.05 (two-tailed) were considered significant. Analyses were carried out using SPSS (SPSS for Windows, version 16.0, 2008, Chicago, IL).

Ethics

This study was conducted in accordance with French legislation and was approved by the national commission of computing and liberties. Due to the retrospective character of this study, approval from the ethics committee was not needed for this non-interventional study based on anonymized data and written consent was not needed.

Results

Over the study period, there were 96,650 births (22 weeks of gestation onward) in the Southern Reunion Island. There were 1,775 preeclampsia cases (incidence 1.8%). Multiple pregnancies (n = 100) were excluded from the study. Among the 1675 singleton preeclamptic pregnancies, 808 were nulliparous (48.2%) and 867 multiparous, among which 14.4% (125/867) presented a RPE and 85.6% (742/867) a first occurrence (Fig. 1).

Baseline clinical data are displayed in Table 1. Mean maternal age was 31.6 ± 5.3 years in the RPE group and 32.2 ± 6.1 years in controls. There was no difference between the two groups concerning parity, BMI, socio-economic status, educational attainment or geographical origins.

Table 2 describes pregnancy characteristics: antenatal follow-up was similar and appropriate according to French recommendations (number of prenatal visits, ultrasonographies, timing for the 1st ultrasound). The prevalence of diabetic patients was similar in both groups. Chronic hypertension was a strong risk factor associated with RPE (OR 2.05 [1.30–3.23], p = 0.002). RPE patients were more likely to develop early onset PE (OR 1.69 [1.15–2.48], p = 0.007). Obviously, the early onset of the disease induced more corticoid treatment in the group with RPE (OR 1.52 [1.03–2.25], p = 0.035). Nevertheless, hospitalization rate, and complications such as HELLP syndrome, eclampsia, or abruptio placentae were comparable within groups.

Table 3 depicts the delivery mode and neonatal characteristics. Among 867 pregnancies, there were 812 live born children, 116 of which from mothers with RPE and 696 from mothers with a first episode. No differences were observed between these two groups with regards to foetal or neonatal mortality.

Compared to women with a first occurrence of preeclampsia, RPE women had a slightly shorter gestational age at delivery (34.1 weeks vs 34.7, not significant) though they were not at higher risk of having premature babies (< 37weeks). RPE patients were more likely to have a history of C-section compared to patients in the control group (65 (77.3%), vs 159 (36.8%), p < 0.001, respectively). Although vaginal delivery was encouraged after C-section, RPE patients had higher C-section rates (71.8% and 60.9%, respectively, OR 1.63 [1.06–2.51], p = 0.024), On the contrary, labour induction was significantly reduced in RPE group (0.50 [0.33-0.77], p = 0.001), possibly contributing to shorter time between rupture of membranes and delivery in this group (0.79 ± 1.95 h instead of 2.24 ± 7.37, p = 0.036). C-sections performed for threatening maternal conditions were more frequent in RPE women than in controls (OR = 2.57 [1.28–5.6], p = 0.008), whereas C-sections for foetal distress were more necessary in *de novo* preeclamptic women (17.2% vs 6%, p = 0.007). There was no significant difference in the rate of C-section for abruptio placentae.

RPE newborns were slightly lighter than newborns from mothers in the control group (−170 g, not significant), but

Table 2
Pregnancy characteristics.

Pregnancy characteristics	Recurrent preeclampsia N = 125 N (%)	First occurrence of preeclampsia N = 742 N (%)	OR [95% CI]	p-value
Number of prenatal consultations (mean ± sd)	7.73 ± 3.08	8.01 ± 3.08		0.368
Patients with less than 3 prenatal consultations	6 (5.0)	29(4.1)	1.25 [0.51-3.08]	0.628
Number of ultrasonographies	4.7 ± 1.6	4.68 ± 1.7		0.59
Date 1 st ultrasonography (weeks : mean ± sd)	11.81 ± 4.34	11.62 ± 4.03		0.645
Weight gain (mean ± sd)	11.27 ± 7.04	11.77 ± 7.03		0.525
Early onset of pre eclampsia (<34 weeks of gestation)	57 (45.6)	246 (33.2)	1 .69 [1.15-2.48]	**0.007***
Gestational diabetes	23 (18.9)	133 (18.3)	1.03 [0.63-1.69]	0.894
Chronic diabetes	6 (5.7)	34 (5.4)	1.06 [0.43-2.58]	0.906
Chronic hypertension	31 (24.8)	103 (13.9)	2.05 [1.30-3.23]	**0.002***
Hospitalization	87 (69.6)	478 (64.4)	1.26 [0.84-1.90]	0.261
Eclampsia	1 (0.8)	11(1.5)	0.54 [0.07-4.19]	0.546
HELLP syndrome	9 (7.2)	37 (5.0)	1.47 [0.65-3.0]	0.42
Abruptio placentae	1 (1.2)	12 (2.8)	0.49 [0.01 ; 3.37]	0.705
Follow-up in outpatient clinic	24 (20.2)	120 (16.8)	1.25 [0.77-2.04]	0.369
Corticoid treatment (fetal maturation)	50 (40.3)	228 (30.8)	1.52 [1.03-2.25]	**0.035***

Significant results, with p-value <0.05, are followed by an asterisk *.

Table 3
Deliveries and Neonatal characteristics (812 liveborn infants, 55 perinatal deaths).

Deliveries and neonatal characteristics	Recurrent preeclampsia Liveborns N = 116 N (%)	First preeclampsia Liveborns N = 696 N (%)	OR [95% CI]	p-value
Delivery gestational age (weeks: mean ± sd)	34.07 ± 3.90	34.74 ± 3.60		0.076
Delivery term <37 weeks of gestation	72 (66.1)	437 (62.8)	1.15 [0.75-1.76]	0.511
Delivery term <33 weeks	35 (32.1)	173 (24.9)	1.43 [0.92-2.21]	0.108
C-section	84 (72.4)	432 (62.0)	1.63 [1.06-2.51]	**0.024***
Indication for C-section:				
• Maternal indication[1]	75 (89.2)	330 (76.4)	2.57 [1.28-5.6]	**0.008***
• Fetal distress	5 (6.0)	76 (17.6)	0.29 [0.10-0.71]	**0.007***
• Abruptio placentae	1 (1.2)	12 (2.8)		NS
• Breech	1 (1.2)	11 (2.5)		NS
• Other	2 (2.3)	3 (0.7)		NS
Labour induction	34 (29.1)	320 (44.8)	0.50 [0.33-0.77]	**0.001***
Post partum haemorrhage[2]	1/83 (1.2)	26/576 (4.5)	0.26 [0.03-1.93]	0.155
Birth weight (g) mean ± sd	2046.87 ± 894.83	2215.81 ± 859.92		0.058
Low birth weight <2500g	72 (66.1)	433 (62.2)	1.18 [0.77-1.81]	0.440
Very low birth weight <1500 g	37 (33.9)	155 (22.3)	1.79 [1.16-2.77]	**0.008***
Small for gestational age	35 (32.1)	180 (25.9)	1.36 [0.88-2.10]	0.170
1-min Apgar score < 7	12 (11.0)	126 (18.2)	0.56 [0.30-1.05]	0.066
Infant respiratory distress syndrome	18 (16.5)	78 (11.2)	1.57 [0.90-2.74]	0.112

	RP All births N = 125 (%)	Controls All births N = 742 (%)	OR [95% CI]	p
- Liveborn	116 (92.8)	696 (93.8)		
- Perinatal mortality	9 (7.2)	46 (6.2)	1.17 [0.52-2.4]	0.33
• In utero fetal death	6	23	1.58	0.328
• Medical termination of pregnancy	2	5	2.4	0.284
• death 0-6 days	1	8	0.74	0.77
• death 7-28 days	0	10		
Fetal sex				
• Girl	68 (54.4)	376 (50.7)	1.15 [0.77-1.73]	0.490
• Boy	57 (45.6)	366 (49.3)		

NS = not significant.
Significant results, with p-value <0.05, are followed by an asterisk *.
[1] Maternal indications for C-sections were : a history of two C-sections or more or a history of myomectomy, failed induced labour, prolonged labour, cephalopelvic disproportion, maternal hemorrhage (including uterine rupture), maternal infection, acute genital herpes during labour, HELLP syndrome, acute fatty liver of pregnancy.
[2] item recorded in the data base since 2005 only.

presented more very low-birthweights (< 1500 g) (33.9% vs 22.3%, OR 1.79 [1.16–2.77], p = 0.008). It is of note that *de novo* preeclamptic newborns presented worse 1-min APGAR scores than RPE babies (p = 0.06).

Comment

In this case-control study over 17.5 years, we reported a 14.4% rate of recurrent preeclampsia, which aligns our results with previously published rates. [15–17]

Main findings

We put into light the following aspects: compared to women with a first episode of PE, RPE women had a higher risk to present with prior chronic hypertension, to experience early onset preeclampsia, to have C-sections for maternal indications (given the higher rate of history of C-section as well), and to give birth to lighter newborns. Nonetheless, in our population of recurrent preeclampsia, there was no evidence for a higher exposure to maternal complications such as HELLP, eclampsia, abruptio placentae or post-partum haemorrhage in subsequent episodes of preeclampsia, nor was there any more in utero foetal death, neonatal or infant death or infant respiratory distress syndrome.

Interpretation

Results from previous studies concerning perinatal outcomes of recurrent preeclampsia are controversial, and diverge, and this can be explained by heterogeneous methodologies. The conflicting results may also be due to lack of clear understanding of the pathogenesis of PE despite the availability of theories about the disease. [18]

For his part, Mendilcioglu [19] stated that women with RPE experienced slightly more foetal loss compared to women with PE who had a prior normotensive pregnancy (19% versus 4.7%), though it was not significant (OR 5.77 [0.84–39.54]). He also found a higher rate of C-section in RPE group. On the contrary, for Cormick [11], RPE was associated with more severe associated morbidities, such as preterm birth, abruptio placentae and fetal death.

Early onset of preeclampsia has also been described, as Sibai reported in his study that among the patients with a history of preeclampsia, who developed a recurrence, one third occurred <28 weeks. [20]

In another study, [21] women with prior PE who developed severe RPE had a significantly lower mean gestational age at delivery as compared to nulliparous women with severe disease (34.8 ± 4.1 vs 37.1 ± 3.6). By contrast, in our study, delivery gestational age was similar (34.07 ± 3.9 weeks of gestation in PE and 34.74 ± 3.6 in first preeclampsia).

Our results also differ from Chen's, [10] who observed babies with higher birthweights in recurrent preeclampsia. Nonetheless, in his study, patients with more severe diseases, such as eclampsia or HELLP syndrome (more likely to have smaller babies), were excluded. This may introduce a bias. In his study, Chen compared the outcomes of earlier and subsequent episodes of preeclampsia in the same patients as well. The incidence of maternal and infant perinatal complications did not differ between the two pregnancies. Van Rijn found no relationship between RPE and severity of the disease in first pregnancy [16]. In our study, we did not have sufficient data to compare preceding and actual episode of PE in patients with a recurrence of the disease. Nevertheless, management of patients with RPE is more complicated than multiparous with first PE. Indeed, we deal with patients who may already have a child born prematurely because of preeclampsia for the first pregnancy, and who may live the same experience a second time, with 7.2% risk to have in utero fetal death, medical termination of pregnancy or neonatal death before 28 days. Moreover, the higher rate of C-section may grieve their obstetrical prognosis for future pregnancies.

In a recent study [22] comparing women with a history of preeclampsia with or without preeclampsia in the index pregnancy, there was no difference concerning the rate of eclampsia and HELLP syndrome. However, the group with RPE presented with increased incidences of C-sections, preterm births, small sized babies and more admissions to neonatal unit, including a higher rate of intraventricular hemorrhage. Although we do not compare similar groups (as said earlier, they compared women with a history of preeclampsia, with or without preeclampsia in the index pregnancy, whereas we compared women with preeclampsia in the index pregnancy, with or without a history of preeclampsia), it is interesting to see the outcomes of subsequent pregnancy, after a history of preeclampsia. This emphasizes the fact that women with a history of preeclampsia should be monitored intensively in their subsequent pregnancies.

Indeed, two recent meta-analyses support consistent two- to three-fold risk for future development of hypertension, two-fold risk for overall cardiovascular disease [23] and 1.19 increased risk of developing venous thromboembolism [24] in women with RPE as opposed to women with a single episode of PE. Besides, risk of subsequent cardiovascular disease death was notably higher among women with onset of preeclampsia by 34 weeks of gestation (hazard ratio: 9.54 [95% CI: 4.50–20.26]) [25]. Although it is unclear whether preeclampsia is a causative or an associated factor of cardiovascular risk, it represents an opportunity for implementing cardiovascular disease prevention at a relative young age [6].

Chronic hypertension has been previously implicated as a risk factor for developing RPE, [7,16,17,26] and this is consistent with our findings. The risk of recurrence was associated with the outcome of the first pregnancy and rose with incidences of preterm birth, severe or complicated eclampsia, HELLP syndrome, or fetal growth restriction [11]. Maternal contributing factors such as obesity, insulin resistance and renal disease have also been linked [15]. In other studies, an inter pregnancy interval longer than 4 years (compared to <2 years and 2–4 years) also increased risk of recurrent RPE. Studies have shown that this was often associated with a change of partner, [27,28], but also loss of immunologic adaptation that protected the mother from recurrence of preeclampsia after delivery over time.16]

Limitations and strengths

Specific limitations of our study included the unavailability of information on some risk factors for preeclampsia such as inter-pregnancy interval and partner changes. Information about aspirin therapy was not recorded in our database neither, nonetheless, in our regional protocol, all women having experienced a preeclampsia, benefited from an aspirin therapy during following pregnancies.

Moreover, although the extended period of the study allowed us to collect a large number of patients, the inconvenient was the changes of obstetrical and neonatal management guidelines, which may lead to a non-uniformity of outcomes.

The strength of our study was the large size of our population. All preeclamptic women in the Southern part of Reunion Island were referred to the tertiary care maternity of Saint Pierre University Hospital, where the data were extracted. The Southern part represents 40% of the deliveries of the Island, and our findings can probably be extrapolated to the population of the whole Island. Our study tips the balance in the favour of studies describing more severe recurrent preeclampsia.

Conclusion

Recurrent preeclampsia in multiparous women was in some aspects more severe than a first occurrence of preeclampsia, with a higher rate of early onset preeclampsia, and more offspring with very low birthweight. Chronic hypertension is an important trigger and should be monitored closely in women with a history of preeclampsia. Therefore, to reduce adverse perinatal outcome related to preeclampsia, future research and prevention efforts for recurrent preeclampsia should focus on women who experienced preeclampsia in a prior pregnancy. Particularly, since risk of subsequent cardiovascular disease death is higher among women with early onset of preeclampsia, early preventive cardiovascular measures should be undertaken in women with recurrent preeclampsia.

Contribution to authorship

PYR and MB conceptualized and designed the study. PYR participated in the acquisition of data and conducted the statistical analyses. PLT and PYR contributed to the interpretation of data, and drafted the initial manuscript. SI, CD, AO, CS critically reviewed the manuscript. All authors read and approved the final manuscript, and accept responsibility for the paper as published.

Details of ethics approval

No ethical approval was required for this study.

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