Risk factors for early and late onset preeclampsia in Reunion island: Multivariate analysis of singleton and twin pregnancies. A 20-year population-based cohort of 2120 preeclampsia cases.

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ABSTRACT

Objectives: To develop a multivariate model for risk factors specific to early onset preeclampsia (EOP) and late onset preeclampsia (LOP) in our entire population (singleton and twin pregnancies).
Material and methods: 20 year-observational population-based historical cohort study (2001-2020). All consecutive births delivered at the Centre Hospitalier Universitaire Hospitalier Sud Reunion's maternity. A standardized validated epidemiological perinatal data base.
Results: During the 20-year period, there were 81,834 pregnancies and 83,555 infants born, 1232 dichorionic and 350 monochorionic twin pregnancies. There were 2120 cases of preeclampsia, of which 2001preeclamptic singleton pregnancies and 119 twin pregnancies (incidence 7.5% in twin pregnancies vs 2.5% singletons, OR 3.0, p<0.001). Independent risk factors for EOP and LOP in a multivariate model (controlling for the two major confounders: namely maternal ages -both risks for EOP and LOP- and maternal pre-pregnancy BMI – specific risk factor for LOP) were: history of preeclampsia (aOR 11.7 for EOP, 7.8 for LOP, p < 0.0001), chronic hypertension (aOR 7.3 for EOP, 3.9 for LOP, p < 0.0001), history of perinatal death (aOR 2.2 for EOP, p < 0.0001 and 1.48 for LOP, p= 0.007), primipaternity (aOR 3.0 for EOP and 3.6 for LOP, p = 0.001), dizygotic twin pregnancies (aOR 3.7 for EOP, p < 0.0001 and 2.1 for LOP, p = 0.003), monozygotic twin pregnancies (aOR 3.98 for EOP, p = 0.003 and NS for LOP), ovulation induction (aOR 5.6 for EOP, p = 0.004 and NS for LOP), and in vitro fertilization (aOR 2.8 for EOP, p = 0.05 and NS for LOP). Specific to LOP and NS for EOP: renal diseases (aOR for LOP 2.9, p= 0.007) and gestational diabetes mellitus (aOR 1.2, p= 0.04).
Conclusions: Maternal ages over 35 years**,** chronic hypertension , history of preeclampsia, ovulation induction, in vitro fertilizations, history of perinatal deaths and twin pregnancy (in our experience, especially mono zygotic twin pregnancies) are significant risk factors for EOP. New paternity is an independent factor for both EOP and LOP.

Keywords
Preeclampsia, epidemiology, early onset preeclampsia, late onset preeclampsia, twin pregnancies, monozygotic twins, dizygotic twins.

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Abbreviations:
EOP: early onset preeclampsia
LOP: late onset preeclampsia
ppBMI: pre-pregnancy maternal body mass index
GDM: gestational diabetes mellitus
CH: chronic hypertension
HP: history of preeclampsia in a preceding pregnancy
FGR: fetal growth restriction
SGA: small for gestational age
IVF: in vitro fecundation fertilization
ATCD: antecedent
MZ monozygotic twins
DZ dizygotic twins

INTRODUCTION

Reunion island belongs to locations where early onset preeclampsia (EOP) appeared to have a very high incidence (31% of our preeclampsia cases, PE) compared with late onset preeclampsia (LOP) [1-3]. Because of the high frequency of this preeclampsia phenotype, we decided more than 20 years ago to start a very detailed perinatal database in addition to the mandated regular perinatal outcome collection. In our first paper [1], we confirmed the high rate of EOP which was for us really a surprise as compared with international literature [1]. Over the last 5 years we have published several epidemiological studies on this islander (epidemiologically "captive") population, analysing specifically risk factors for EOP and LOP [4-9]. The five first studies [4-8] were focused only on singleton pregnancies, the last one was on twin pregnancies [9].
These studies present in our opinion important epidemiologic data since (1) we are sure to have considered all preeclampsia cases of the south of the island of Reunion (850,000 inhabitants, 380,000 in the south) during these 20 years, as there is only one university hospital, level 3, allowed to care and deliver PE pregnancies. Therefore, these data represent a true population-based cohort collected through a specific database that differentiated between EOP and LOP.
The first risk factor study [4], 15 year cohort (1,397 PE cases), revealed that EOP women were older than LOP ones; while primigravidas and primiparas, typically younger than multiparous women, were more prone to develop LOP. Women older than 35, IVF-ICSI, chronic hypertensive, 'thrombophilia' (see methods), thyroid diseases were more prone to EOP (we did not analyse history of previous PE in multiparas). Although not statistically significant, in this first study (comparisons between EOP vs LOP), obese women were more prone to LOP.
The second risk factor study, 18 year cohort (1,736 cases of PE) [5], concluded that chronic hypertension and history of preeclampsia were the strongest risk factors for EOP. Age over 35 years, BMI $\geq$ 35 kg/m² and, again, primiparity were rather associated with LOP. However, analyzing by increment of 5 kg/m² for BMI, rising BMI was only associated with LOP (and very poorly with EOP), and that, controlling for maternal ages and booking/pre-pregnancy BMI, diabetes was not an independent risk factor neither for EOP nor for LOP. We concluded that metabolic factors, other than diabetes, associated with pre-pregnancy maternal corpulence were specifically associated with LOP.

The third study [6] was a kind of confirmation, 18 year cohort (1,736 cases of PE). Being surprised by some results of the preceding studies, namely that EOP women were older than EOP and that primiparas were more prone to LOP (findings also confirmed by a study we shared with the University Maternity of Antananarivo, Madagascar [10]), we decided to test if it was not the international cut- off of 34 weeks between EOP and LOP that could explained our results. In this study [6], we tested different possible cut-offs (CO) at 30, 32, 34 and 37th week of gestation: still primigravid were more prone to LOP (C30 to CO37), women with EOP had a lower BMI as compared with LOP at CO34 and CO37. Gestational diabetes mellitus was not associated with LOP at any cut-off (aOR 1.07, NS) but was 'protective' against EOP from CO30 to CO34 (aOR 0.42, 0.61 and 0.73, respectively, P < .001). This protective effect disappeared at CO37. Chronic hypertension and history of preeclampsia were both EOP and LOP risks but with a much stronger effect for EOP. We concluded that the 34th week of gestation appeared to provide a reasonable cut-point to differentiate between EOP and LOP.

The fourth study [7], 19 year cohort (1,814 cases of PE) concluded that major risks for EOP were older age (over 35 years), chronic hypertension, history of previous PE, thrombophilia, induction of ovulation (without IVF). LOP women were still older than EOP women with primiparas being also more prone to LOP, as well as women with renal disease. LOP women were more prone to have a higher BMI than EOP.
In the fifth study [8], we had the curiosity to verify what could be the remaining risk factors in a population where major

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risk factors for EOP (chronic hypertension, history of preeclampsia mainly) and other 8 risk factors (multiple pregnancies, pre-existing diabetes mellitus, chronic hypertension, history of previous preeclampsia, 'thrombophilia', renal or thyroid disease, and smoke) were excluded. Surprising, we found that this population of "women without morbidities and significant obstetrical past" comprised 72% of a female reproductive community, but they still comprised 63% of all preeclampsia cases (PE incidence of 2.1% vs 2.5% in the general population) [8]. Our conclusions were that "In this 'knock-out' (KO) population, we confirmed that overweight and different classes of obesities were linearly and increasingly linked with only LOP, and disconnected with EOP. New paternity was also an independent factor for both EOP and LOP in multiparas[8].

Finally, our sixth study [9] (a 20-year cohort of 2120 PE cases) explored the association between EOP and LOP and twin pregnancies: 1232 dizygotic (DZ) and 350 monozygotic (MZ) twin pregnancies. We confirmed what is well known in the literature that for twin pregnancies the relative risk of PE was nearly 3 as compared with singleton pregnancies. There were in total 2120 preeclampsia cases (incidence 2.6%), of which 2001 PE singleton pregnancies and 119 twin pregnancies (incidence 7.5% in twin pregnancies vs 2.5% singletons, OR 3.0, $p<0.001$). The EOP proportion of PE cases was similar in singleton and DZ twin pregnancies : 32% (respectively 641/2001, 32.0% and 26/84, 31.0%, crude OR 0.95, $p=0.41$ DZ-EOP vs singleton EOP). Nevertheless, we were surprised to find that MZ twin pregnancies were a paramount risk of EOP: in MZ pregnancies when preeclampsia occurred, two third of cases were EOP (17/26, 65.4%, crude OR 4.0 MZ-EOP vs singleton-EOP, $p< 0.0001$). Surprisingly also, and without explanation, in our 26 MZ preeclamptic twins 73% newborns were females (19 pairs/26), while in normotensive MZ twins 51% were female infants (in DZ preeclamptic twins 49% were female).

The purpose of this study is, firstly to upgrade all our calculations using the 20 year cohort (2120 preeclampsia cases of which 119 in twin pregnancies) and, secondly, to develop a multivariate model controlling for the two major confounders: Maternal age (both risks for EOP and LOP) and maternal pre-pregnancy BMI (major risk factor for LOP [5]) with all the detected other risk factors in singleton and in twin pregnancies.

MATERIAL AND METHODS

From January 1st, 2001, to December 31, 2020, the hospital records of all women delivered at the maternity of the University South Reunion Island (ap. 4 300 births per year) were abstracted in standardized fashion. The study sample was drawn from the hospital perinatal database which prospectively records data of all mother-infant pairs since 2001, and all normotensive singleton pregnancies included as reference. Information is collected at the time of delivery and at the infant hospital discharge and regularly audited by appropriately trained staff. These epidemiological perinatal data base which contained information on obstetrical risk factors, description of deliveries and neonatal outcomes. For the purpose of this study records have been validated and have been used anonymously. Additionally, during all the prenatal follow-up during pregnancy, and as participants in the French national health care system, all pregnant women in Reunion Island have their prenatal visits, biological and ultrasonographic examinations, and anthropological characteristics recorded in their maternity booklet before coming at the maternity for delivery. Preeclampsia, gestational hypertension and eclampsia were diagnosed according to the definition issued by the International Society for the Study of Hypertension in Pregnancy (ISSHP) relatively to the guidelines in force at the year of pregnancy.

Design and study population

The maternity department of Saint Pierre hospital is a tertiary care centre that performs about 4 300 deliveries per year, thus representing about 80% of deliveries of the Southern area of Reunion Island, but is the only level 3 maternity (the other maternity is a private level 1 hospital, which is not allowed to follow/deliver preeclamptic pregnancies). Reunion Island is a French overseas region in the Southern Indian Ocean. Virtually the whole population has then access to health care. This is provided free of charge by the French healthcare system, which combines freedom of medical practice with nationwide social security.

Definition of exposure and outcomes

From 2001 to 2020, we are sure that our tertiary unit have covered all multiple pregnancies delivered in the Southern part of the island.

SGA defined as gestational age-adjusted birth weight < 10th centile according to normal tables for our specific population (both sex together).

Renal diseases were defined as patients with known pre-existing nephropathies without hypertension (glomerulopathies, tubulopathies, renal failure, diabetic nephropathies). Urological pathologies were excluded.

Thyroid diseases were defined as hypo/hyperthyreoidism , goitre, thyroiditis, prior thyroidectomy. Thrombophilias were defined as antiphospholipid syndrome, protein C or protein S deficiency , Factor 5 Leyden or other coagulation

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factors deficits at any time they were reported in the records (these were not systematically screened in all women as in a case-control study).

Preeclampsia was defined according to the World Health Organization recommendations [11] and the International Society for the study of Hypertension in Pregnancy [12] 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 hours). Early onset preeclampsia (EOP) was defined as preeclampsia that resulted in the birth before 34 week's gestation. LOP was defined as preeclampsia associated with birth > 34 week's gestation.

The "primipaternity" item (changing father for the index pregnancy) has been added in the database in 2018 and has been prospectively recorded since then. It is the sum of all primigravidas (and not primiparas) plus multiparous having changed partner for the index pregnancy. For the other years (2001-2017), we retrospectively looked at all free commentaries (possible in each record) for "changing father, changing paternity, new father, new partner etc…." in multiparas (therefore probably non-exhaustive), but we retrieved 780 cases .

Screening of GDM is systematically made in all pregnant women in the 2nd trimester: until 2016 it was the O'Sullivan test (50g glucose, blood glucose level after 1 hour). The threshold for hyperglycemia being 1.4 g/l. Since 2016, this test has been replaced in all women by a fasting glycemia in the first trimester, the threshold for positivity being 0.92 g/l, and the glucose tolerance test (GTT) at 24-28 weeks in all pregnant women. Those who have no GTT are only those who have a 1st trimester blood glucose over 1.26 g/l, these one being considered as Type 2 diabetes.

Statistical analyses

Data is presented as numbers and proportions (%) for categorical variables and as mean and standard deviation (SD) for continuous ones. Comparisons between groups were performed by using χ^2-test; odds ratio (OR) with 95% confidence interval (CI) was also calculated. Paired t-test was used for parametric and the Mann-Whitney *U* test for non-parametric continuous variables. P-values <0.05 were considered statistically significant. Epidemiological data have been recorded and analysed with the software EPI-INFO 7.1.5 (2008, CDC Atlanta, OMS), EPIDATA 3.0 and EPIDATA Analysis V2.2.2.183. Denmark

Further, to validate the independent association of consensual risk factors on EOP or LOP we realized a multiple regression logistic model. Variables associated with in bivariate analysis, with a p-value below 0.1 or known to be associated with the outcome in the literature were included in the model. A stepwise backward strategy was then applied to obtain the final model. The goodness of fit was assessed using the Hosmer-Lemeshow test. A p-value below 0.05 was considered significant. All analyses were performed using MedCalc software (version 12.3.0; MedCalc Software's, Ostend, Belgium).

Ethical approval

This study was conducted in accordance with French legislation. As per new French law applicable to trials involving human subjects (Jardé Act), a specific approval of an ethics committee (comité de protection des personnes- COP) is not required for this non-interventional study based on retrospective, anonymized data of authorized collections and written patient consent is not needed. Nevertheless, the study was registered on UMIN Clinical Trials Registry (identification number is UMIN000037012).

RESULTS

During the 20-year period, there were 106,580 births in the South of the Reunion Island of which 83,555 (78.4%, 81,834 pregnancies) in the University maternity of Saint-Pierre (the other births occurred in a single private clinic, level 1, not allowed to manage preeclamptic pregnancies and their births). During the period, we had 2120 preeclampsia (incidence 2.6% in the University maternity), of which 2001 preeclamptic singleton pregnancies and 119 twin pregnancies (incidence 7.5% in twin pregnancies).

Table 1 gives an overview of our population. Mothers with twin pregnancies were older than singletons (27.8 vs ≈ 29, p = 0.0006), had more prenatal visits (9.3 vs 8.7, p< 0.0001), much more ultrasounds 7.8 (MZ), 5.9 (DZ) vs 4.4, p< 0.0001 and a much more higher rate of hospitalizations in the maternity high risk clinic: 60% (MZ), 50% (DZ) vs 15.2% in singletons, p< 0.0001. Adolescents were underrepresented in twin pregnancies (OR 0.31 and 0.62), while women of 35+ years had more twin pregnancies (OR 1.3 and 1.4, p< 0.0001). Women with twin pregnancies had a tendency to have a higher pre-pregnancy BMI (+ 0.6 kg/m²) than singletons but only DZ pregnancies were significantly overweight or obese (respectively OR 1.15 and 1.21, p= 0.02 and > 0.0001). Similarly only DZ pregnancies had a tendency to have more chronic hypertension (OR 1.37, p= 0.07), gestational diabetes (OR 1.18, p= 0.01) or history of perinatal deaths in multiparas (OR 1.66, p= 0.0001). Only DZ pregnancies also had a very high rate of IVF and ovulation induction pregnancies (OR 40 and 38, p< 0.0001).

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Table 1. Maternal and pregnancy characteristics

	Controls singleton pregnancies N= 80,187 (%)	**Twin dizygotic N= 1232 pregnancies (%)**	**DZ vs ctrls OR [95% CI] (%)**	**Twin monozygotic N= 350 (%)**	**MZ vs ctrls OR [95% CI] (%)**
Maternal age (years : mean ± sd)	27.8±6.6	29.6 ± 5.9	P < 0.0001	28.6 ± 7.0	0.0006
Gravidity ± sd	2.85±1.95	2.87 ± 1.94	0.67	3.15 ± 2.2	0.003
Parity ± sd	1.29±1.5	1.27 ± 1.5	0.74	1.51±1.8	0.008
prenatal visits mean ± sd	8.77±2.8	9.2±2.9	P < 0.0001	9.3±3.3	P < 0.0001
Ultrasonographies mean ± sd	4.4±1.7	5.9±2.1	P < 0.0001	7.8±3.4	P < 0.0001
Hospitalizations at risk clinic	12,215 (15.2)	618 (50.1)	5.6 [5.0-6.3} P < 0.0001	211 (60.3)	8.4 [6.8-10.5] P < 0.0001
Primiparity	29,920 (37.3)	486 (39.4)	1.09 P= 0.13	116 (33.3)	0.84 P= 0.12
adolescents	3277 (4.1)	16 (1.3)	0.31 [0.19-0.51] P < 0.0001	9 (2.6)	0.62 [0.32-1.21] P=
Grand Multiparous women (≥5)	6532 (8.2)	104 (8.2)	1.04 P=0.35	40 (11.4)	1.46 [1.05-2.0] P = 0.01
Age ≥ 35 years	14,198 (17.7)	271 (22.1)	1.31 [1.15-1.5] P < 0.0001	81 (23.3)	1.4 [1.1-1.8] P < 0.0001
Marital status : Single	29,343 (36.7)	313 (25.6)	0.59 [0.52-0.67] P < 0.0001	110 (31.7)	0.80 [0.64-0.99] P =0.05
Years school ≥ 10	45,364 (58.8)	752 (65.3)	1.32 [1.17-1.49] P < 0.0001	195 (58.9)	1.0 P = 0.96
Pre-pregnancy BMI (mean ± sd)	24.8±6.0	25.4±6.4	0.001	25.3 ± 6.45	0.13
ppBMI ≥ 25 kg/m²	30,399 (39.5)	494 (42.8)	1.15 [1.02-1.29] P= 0.02	145 (43.5)	1.18 P= 0.13
ppBMI ≥ 30 kg/m²	13,814 (17.9)	241 (20.9)	1.21 [1.05-1.39] P < 0.0001	62 (18.6)	1.09 P = 0.25
Renal diseases	217 (0.3)	1 (0.08)	0.29 P=0.10	3 (0.8)	3.2 [0.80-8.8] P=0.07
Thyroid diseases #	1100 (1.4)	30 (2.4)	1.8 [1.2-2.6] P=0.007	12 (3.4)	2.5 [1.4-4.6] P=0.0005
In vitro fecundation	547 (0.7)	269 (21.8)	40 [34-47] P < 0.0001	3 (0.8)	1.25 P=0.34
Ovulation induction	211 (0.3)	112 (9.1)	38 [30-48] P < 0.0001	4 (1.1)	4.3 [1.4-10.8] P=0.03
Chronic hypertension	1290 (1.6)	27 (2.2)	1.37 [0.93-2.0] P= 0.07	6 (1.7)	1.06 P= 0.43
Gestational diabetes	9283 (11.7)	165 (13.5)	1.18 [1.01-1.39] P= 0.01	54 (15.6)	1.4 [1.04-1.9] P < 0.0001
Pre-existing diabetes	1256 (1.8)	19 (1.5)	0.98 P=0.47	5 (1.7)	0.96 P= 0.80
History preeclampsia (multiparas)	812 (1.6)	10 (1.3)	0.83 P= 0.55	3 (1.1)	0.8 P=0.69
History of perinatal deaths (multiparas)	2576 (4.4)	63 (7.0)	1.66 [1.28-2.15] P= 0.0001	10 (3.7)	0.84 P= 0.60

goitre, hypo-hyperthyroidy, thyroidectomy, thyroid node, thyroiditis

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Table 2 shows the decreasing rankings of CRUDE odds ratios of risk factors for all preeclampsia and for EOP . For all preeclampsia the ranking was: 1) history of preeclampsia in multiparas, 2) chronic hypertension, 3) renal diseases 4) MZ and DZ twins etc…
For EOP, the ranking became: 1) MZ twin pregnancies, 2) ovulation induction pregnancies, 3) history of previous perinatal deaths in multiparas, 4) chronic hypertension and previous history of preeclampsia (gestational diabetes being protective towards EOP, Or 0.69, p=0.004).
Table 3: Considering the logistic model with the outcome EOP some major risk factors remained as compared with crude odds ratios;1) history of preeclampsia (1.6% of our multiparas), aOR 11.6, 2, chronic hypertension (1.6% of all our population) aOR 7.4, p< 0.0001, 3) pregnancies after ovulation induction aOR 4.8, p=;0.03,. 4) Quite similar MZ twin pregnancies (0.85% of all our pregnancies) 3.98, and DZ twin pregnancies (1.5% of our pregnancies), aOR 3.67, both p< 0.001., 6) first pregnancies (28% of our pregnancies: primigravid and multiparas with new father), aOR 3.0, p< 0.0001). In contrast, gestational diabetes (aOR 0.80, 12% of our pregnancies) was not a significant risk for the EOP.

It is of note that both maternal ages (by increment of 5 years of age) and maternal pre-pregnancy BMI (by increment of 5 kg/m²) had a slight constant increasing power (both aOR = 1.03, p= 0.004) on the EOP risk i.e. an increased risk of 2.7% by increment of 5 years of age or 5kg/m² BMI (both coefficient 0.027, coefficients not shown in the Tables).
Table 4. Logistic model with LOP as outcome. Like for EOP (aOR 1.03 for maternal ages as well as for BMI), we still retrieve the constant increasing power of maternal ages and pre-pregnancy BMI but much stronger than for EOP: aOR = 1.04 for maternal ages (This time an increased risk of 4% by increment of 5 years of age, coefficient 0.042) and 1.05 for pre-pregnancy BMI (and an increased risk of 5% by increment of 5kg/m² BMI, coefficient 0.051), both p < 0.0001.

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Table 2. **Crude Odds ratios**. A) On the left ranking of preeclampsia risk (as compared with controls: singleton pregnancies without hypertension) from the highest risk to the lowest. B) on the right, ranking of EOP risk. from the highest risk to the lowest (Reference/control: percentage of EOP in singleton preeclamptics: 32.0%).

Risk factors RANKING FOR PREECLAMSIA RISK	Incidence Preeclampsia (%)	Odds Ratios [95% CI]	p- values	Risk factors RANKING FOR EOP RISK	Percentage of EOP (%)	Odds Ratios [95% CI]	p- values
Atcd preeclampsia (multiparas)	152/811 (18.7)	9.0 [7.5-10.9]	<0.0001	**Monozygotic twins**	17/26 (65.4)	4.0 [1.8-10.2]	< 0.001
Chronic hypertension	209/1289 (16.2)	7.55 [6.5-8.8]	<0.0001	**ovulation induction**	9/16 (56.3)	2.7 [1.01-7.3]	0.02
Renal diseases	26/217 (12.0)	5.3 [3.5-8.0]	<0.0001	**Atcd perinatal deaths (multiparas)**	57/116 (49.1)	2.05 [1.4-3.0]	< 0.001
Monozygotic twins	26/350 (7.4)	3.1 [2.0-4.6]	<0.0001	**Atcd preeclampsia (multiparas)**	67/155 (43.2)	1.6 [1.15-2.2]	0.002
Dizygotic twins	84/1232 (6.8)	2.85 [2.3-3.6]	<0.0001	**Chronic hypertension**	85/209 (40.6)	1.45 [1.08-1.9]	0.005
Pre-existing diabetes	80/1255 (6.4%)	2.65 [2.1-3.3]	<0.0001	**Gestational diabetes**	79/320 (24.6)	0.69 [0.53-0.90]	0.004
Ovulation induction	16/301 (5.3)	2.19 [1.3-3.6]	0.002	**All singleton preeclamptics**	**641/2001 (32.0)**	**Reference**	-
IV fecundation	42/746 (5.6)	2.3 [1.7-3.2]	<0.0001	**Thrombophilias**	7/14 (50.0)	2.1 [0.74-6.1]	0.12*
Thrombophilias	14/278 (5.0)	2.06 [1.2-3.5]	0.006	**Renal diseases**	11/26 (42.3)	1.55 [0.69-3.4]	0.13
Atcd perinatal deaths (multiparas)	116/2655 (4.4)	1.78 [1.47-2.1]	<0.0001	**Thyroid diseases**	16/42 38.1%	1.3 [0.69-2.4]	0.20
Thyroid diseases	42/1100 (3.8)	1.55 [1.1-2.1]	0.003	**Smoking**	62/180 (34.4)	1.1 [0.80-1.5]	0.25
Gestational diabetes	320/9283 (3.4)	1.4 [1.2-1.6]	<0.0001	**Dizygotic twins**	26/84 (30.9)	0.95	0.41
Primipaternity	747/22,662 (3.3)	1.33 [1.2-1.4]	<0.0001	**IV fecundation**	13/42 (30.9)	0.95	0.44
primigravidity	691/21,898 (3.2)	1.27 [1.16-1.38]	<0.0001	**Primipaternity**	224/747 (30.0)	0.91	0.15
All singleton pregnancies	**2001/80,187 (2.5)**	**Reference**	-	**primigravidity**	202/691 (29.3)	0.88	0.09
Smoking	180/9923 (1.8)	0.72 [0.62-0.84]	<0.0001	**Pre-existing diabetes**	23/80 (28.7)	0.86	0.31

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Table 3. Adjusted Odds ratios. **Outcome: EARLY ONSET preeclampsia EOP**.
Logistic model including singletons and monozygotic & dizygotic twins

Preeclamptic women PE (N= 2001), EOP (N= 641), LOP (N= 1360)
versus controls, normotensive women (N= 78,085)

	Singletons N= 641 EOP aOR	P val	**MZ N= 17/350 aOR**	P val	**DZ N= 26/1232 aOR**	P val
Ovulation induction	**5.6 [1.7-18.3]**	0.004	**4.8 [1.1-20.3]**	0.03	3.1 [0.73-13.1]	0.13
Atcd perinatal deaths	**2.2 [1.5-3.1**	<0.0001	**2.1 [1.45-3.1]**	0.0001	**2.1 [1.5-3.04]**	<0.0001
Atcd Preeclampsia	**11.7 [8.5-16.0]**	<0.0001	**12.3 [8.4-17.0]**	<0.0001	**11.6 [8.4-16.0]**	<0.0001
Chronic HBP	**7.3 [4.1-6.3]**	<0.0001	**7.2 [5.1-10.1]**	<0.0001	**7.4 [5.3-10.3]**	<0.0001
IVF	**2.8 [1.01-7.7]**	0.05	2.1	0.30	1.2	0.72
Primipaternity#	**3.0 [1.7-5.3]**	0.0001	**2.96 [1.6-5.3]**	0.0002	**3.02 [1.7-5.4]**	0.0002
Maternal Age (increment/5 years)	**1.03 [1.01-1.05]**	0.005	**1.03 [1.01-1.05]**	0.001	**1.03 [1.01-1.05]**	0.004
BMI (increment/5 kg/m²)	**1.03 [1.01-1.04]**	0.002	**1.03 [1.01-1.05]**	0.0006	**1.03 [1.01-1.05]**	0.001
Preexisting diabetes	0.82	0.55	0.85	0.64	0.85	0.63
Gest diabetes	0.81	0.20	0.72 [0.52-1.0]	0.06	0.81	0.20
Renal diseases	1.91 [0.66-5.5]	0.23	2.0 [0.7-5.8]	0.20	2.02 [0.70-5.8]	0.19
Thrombophilias	1.66 [0.5-5.5]	0.40	1.9 [0.55-6.1]	0.31	1.8	0.33
smoking	0.90	0.56	0.94	0.73	0.87 [0.6-0.9]	0.45
Atcd abortions	0.96	0.80	1.01	0.93	0.98	0.87
MZ twins	-	-	**3.98 [1.6-9.9]**	**0.003**	**-**	-
DZ twins	-	-	-	-	**3.67 [2.1-6.4]**	**<0.0001**

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Table 4. Adjusted Odds ratios. Outcome: **LATE ONSET preeclampsia LOP.**
Logistic model including singletons and monozygotic & dizygotic twins.

Preeclamptic women PE (N= 2001), EOP (N= 641), LOP (N= 1360)
versus controls, normotensive women (N= 78,085)

	Singletons 1360/80,081 LOP aOR	P val	**MZ twins N= 9/350 aOR**	P val	**DZ twins N= 57/1232 aOR**	P val
Ovulation induction	1.5 [0.37-6.3]	0.56	1.35 [0.2-9.9]	0.76	1.48 [0.4-6.2]	0.58
Atcd perinatal deaths	**1.48 [1.1-1.98]**	0.007	**1.49 [1.07-2.07]**	0.02	**1.48 [1.1-2.0]**	0.007
Atcd Preeclampsia	**7.8 [6.1-10.1]**	<0.0001	**9.1 [6.8-12.0]**	<0.0001	**7.85 [6.1-10.2]**	<0.0001
Chronic HBP	**3.9 [3.0-5.1]**	<0.0001	**3.7 [2.7-5.1]**	<0.0001	**3.9 [3.0-5.1]**	<0.0001
IVF	0.86	0.80	1.4	0.67	0.67	0.51
Primipaternity#	**3.6 [2.5-5.2]**	0.0001	**3.5 [1.6-5.3]**	<0.0001	**3.5 [2.4-5.1]**	<0.0001
Maternal Age (increment/5 years)	**1.04 [1.03-1.06]**	<0.0001	**1.04 [1.03-1.06]**	<0.0001	**1.04 [1.03-1.06]**	<0.0001
BMI (increment/5 kg/m²)	**1.05 [1.04-1.06]**	<0.0001	**1.05 [1.04-1.07]**	<0.0001	**1.05 [1.04-1.06]**	<0.0001
Preexisting diabetes	**1.57 [1.09-2.3]**	0.01	**1.6 [1.1-2.4]**	0.008	**1.6 [1.1-2.3]**	0.01
Gest diabetes	**1.2 [1.01-1.5]**	0.04	**1.2 [1.01-1.5]**	0.04	**1.2 [1.01-1.5]**	0.03
Renal diseases	**2.9 [1.3-6.2]**	0.007	**2.6 [1.07-6.1]**	0.03	**2.9 [1.3-6.3]**	0.006
Thrombophilias	2.0 [0.9-4.7]	0.10	1.5 [0.55-4.3]	0.40	2.0 [0.86-4.7]	0.10
smoking	0.80 [0.62-1.03]	0.09	**0.70 [0.52-0.95]**	0.02	0.80 [0.6-1.04]	0.09
Atcd abortions	1.02	0.83	1.1	0.33	1.1	0.87
MZ twins	-	-	1.44 [0.45-4.6]	0.53	-	-
DZ twins	-	-	-	-	**2.07 [1.3-3.4]**	0.003

In the LOP risk, the adjusted ranking became different than for the EOP risk: MZ twin pregnancies and ovulation induction disappeared as risk factor. In contrast, (not existing in EOP), we see the appearance of renal diseases (AOR 2.9, p= 0.006) , a small association with gestational diabetes mellitus (aOR 1.2, p= 0.03) and little stronger with pre-existing diabetes (aOR 1.6, p= 0.01). DZ twins have still an aOR of 2.1, p= 0.003 (but less than for EOP, aOR 3.67).
Some similarities between EOP and LOP: 1) still history of preeclampsia but much less than for EOP aOR 7.85 (vs 11.6, EOP). 2), also chronic hypertension but again less than for EOP aOR 3.9, $p < 0.0001$ (vs 7.4, EOP). 3) primipaternity aOR 3.5, $p < 0.0001$. 4) appearance of renal diseases (glomerulo-tubulopathies, 0.3% of our pregnancies) aOR 2.9, p= 0.006, which were not significant for the crude OR (Table 3) and for EOP (Table 4).

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5) history of previous fetal deaths aOR 1.48, p= 0.007 (but less than for EOP aOR 2.1). 6) a minor effect of diabetes mellitus: similar with pre-existing diabetes aOR 1.6, p=0.01 and GDM aOR 1.2, p= 0.03.

Figure 1 represents a visualization of the adjusted odds ratios calculated in Tables 3 and 4: independent risk factors for EOP and LOP controlling for the two major confounders: maternal ages (both risks for EOP and LOP) and maternal pre-pregnancy BMI (major risk factor for LOP).
1) specific risk for EOP: monozygotic twins (and in our experience especially female pairs) and pregnancies after ovulation induction . 2) common risk factors between EOP and LOP but with a much higher risk for EOP: chronic hypertension and history of preeclampsia. 3) common risk factors between EOP and LOP but with a similar risk: dizygotic twins, new paternity, history of perinatal deaths. 4) Specific risk for LOP (besides the known effect of overweight and obesity): renal diseases and gestational diabetes mellitus.

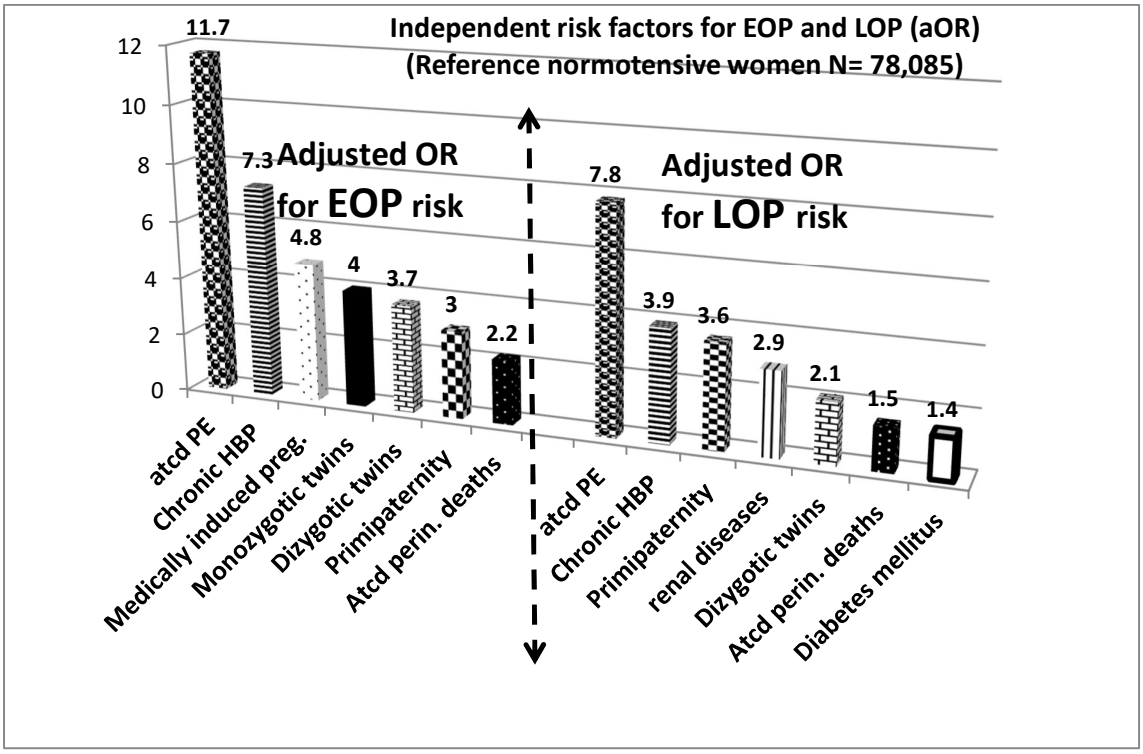

Figure 1. Independent risk factors for EOP and LOP (adjusted odds ratios) controlling for the two major confounders: maternal ages (both risks for EOP and LOP) and maternal pre-pregnancy BMI (major risk factor for LOP). Increment by 5 years of age and by 5 kg/m² for and maternal pre-pregnancy BMI.

DISCUSSION

This study wishes to contribute to epidemiological studies on risk factors for preeclampsia, especially for EOP Our study confirms that major risk factors for EOP are: chronic hypertension , history of preeclampsia, ovulation induction, history of perinatal deaths and possibly twin pregnancies [18,19] (in our experience, especially mono zygotic twin pregnancies).
Regarding prevention of EOP, there is now good evidence that 150 mg of aspirin < 16th week of gestation will halve the risk [16,17] except in patients with chronic hypertension, where no beneficial effect is evident [16]. This prevention may also the rate of the iatrogenic preterm birth by delaying the medical decision to induce the newborns births/perform a caesarean section [20].
Reading the international literature, it seems that an international consensus comprises some 11 risk factors: multiple pregnancies, chronic hypertension, preeclampsia or hypertension in a previous pregnancy, diabetes, nulliparity, renal disease, “Thrombophilias”-anti phospholipid syndrome , maternal age > 40 years, body mass index > 35 kg/m², family history of preeclampsia, assisted reproduction [11-15]. Especially for Lisonkova & Joseph “African-American race, chronic hypertension, and congenital anomalies were more strongly associated with early-onset preeclampsia, whereas younger maternal age, nulliparity, and diabetes mellitus were more strongly associated with late-onset disease.” [12].

Optimal gestational weight gain surveillance in overweight/obese women as prevention of late onset preeclampsia (90% of preeclampsia cases in developed 'Western lifestyle countries).

For the LOP risk, our multivariate model identifies some risk factors common to the EOP risk (Tables 3 and 4 and figure 1): History of preeclampsia, chronic hypertension, history of perinatal death. Renal diseases and gestational diabetes mellitus(small association OR 1.2, p= 0.03) seem to be specific to the LOP risk. But, here, we would like to propose a 'new' promising approach: recently 2 different teams from two different parts of the world (USA and Reunion Island, Indian ocean) [21,22] have described that late-onset preeclampsia (and much less early-onset preeclampsia) is largely and specifically linearly associated with rising maternal Body mass index (BMI). Further research is urgently required in order to properly understand the main drivers and pathways on how the cardiometabolic syndrome leads to late-onset preeclampsia [23]. Importantly, we have recently demonstrated that having a high BMI does not automatically translate in a high risk of term preeclampsia. Obese patients can significantly decrease their risks by fine tuning of their gestational weight gain (GWG) [24-27].

Strengths. The strengths of this study are mostly related to the homogeneity of data in such a large cohort as they were collected in a single center (no intercenter variability) and not based on national birth registers but directly from medical records (avoiding inadequate codes).

The Centre Hospitalier Universitaire Sud-Reunion's maternity (Level 3, European standards of care) is the only public hospital in the southern part of Reunion Island (Indian Ocean, French overseas department). It serves the whole population of the area (ap. 360,000 inhabitants, and 5,100 births per year). With 4,300 births per year, the university maternity represents 82% of all births in the south of the island. But, as a level 3 (the other maternity is a private clinic, level 1), we are sure all the preeclampsia cases as well as all multiple pregnancies were referred to our hospital during the 20 year period. This is therefore a real population-based study.

Weakness. As a limitation of the study, we have to consider the retrospective nature of the study that, although the number of information that is recorded is comprehensive, some characteristics may miss like length of sexual relationship and/or primipaternity. The presence of thrombophilia was not systematically screened in all women (cases and references). However, every time a woman was known to have one of these characteristics, they were scrupulously included in the database. Also the item on partner change was only added to the database in 2018. For the other years (2001-2017), we retrospectively looked at all free commentaries (possible in each record) for "changing father, changing paternity, new father, new partner etc….". We did not test neither interval between pregnancies.

CONCLUSION. This study confirms that maternal ages over 35 years**,** chronic hypertension , history of preeclampsia, ovulation induction, history of perinatal deaths and possibly twin pregnancies (in our experience, especially mono zygotic twin pregnancies) are significant risk factors for EOP, the fearsome early onset form of preeclampsia. It is of note that in both multivariate models for EOP and LOP, we noticed as an independent risk factor : "primipaternity" (i.e the combination of primigravid and multiparas with a new male partner yes/no, without any notion of duration of cohabitation before conception). This approach of paternity may urgently require adequately powered prospective trials as we hypothesize that it should be the new couples with less than 6 months of sexual cohabitation before conception which should be those especially at risk of EOP [28] (and beneficiate of aspirin prophylaxis). Therefore, clinicians should add as a systematic question the inquiry of paternity in all beginning of prenatal visit in any pregnancy and also evaluate the length of sexual cohabitation before conception in case of new father [28].

REFERENCES

1) Iacobelli S, Bonsante F, Robillard PY. Pre-eclampsia and preterm birth in Reunion Island: a 13 years cohort-based study. Comparison with international data. J Matern Fetal Neonatal Med. 2016 Sep;29(18):3035-40. doi: 10.3109/14767058.2015.1114081. Epub 2015 Nov 23. PMID: 26512885.

2) Robillard PY, Dekker G, Iacobelli S, Chaouat G. An essay of reflection: Why does preeclampsia exist in humans, and why are there such huge geographical differences in epidemiology? J Reprod Immunol. 2016 Apr;114:44-7. doi: 10.1016/j.jri.2015.07.001. Epub 2015 Jul 11. PMID: 26253618.

3) Robillard PY, Dekker G, Chaouat G, Elliot MG, Scioscia M. High incidence of early onset preeclampsia is probably the rule and not the exception worldwide. 20th anniversary of the reunion workshop. A summary. *J Reprod Immunol*. 2019;133:30-36.

4) Iacobelli S, Bonsante F, Robillard PY. Comparison of risk factors and perinatal outcomes in early onset and late onset preeclampsia: A cohort based study in Reunion Island. J Reprod Immunol. 2017 Sep;123:12-16. doi: 10.1016/j.jri.2017.08.005. Epub 2017 Aug 24. PMID: 28858635.

5) Robillard PY, Dekker G, Scioscia M, Bonsante F, Iacobelli S, Boukerrou M, Hulsey TC. Increased BMI has a linear association with late-onset preeclampsia: a population-based study. PLoS One. 2019 Oct 17;14(10):e0223888. doi: 10.1371/journal.pone.0223888.

6) Robillard PY, Dekker G, Scioscia M, Bonsante F, Iacobelli S , Boukerrou M, Hulsey TC. Validation of the 34-week gestation as definition of late onset preeclampsia:Testing different cutoffs from 30 to 37 weeks on a population-based cohort of 1700 preeclamptics. Acta Obstet Gynecol Scand. 2020 Mar 16. doi: 10.1111/aogs.13846.

7) Robillard PY, Dekker G, Scioscia M, Bonsante F, Iacobelli S, Boukerrou M, Hulsey TC. The blurring boundaries between placental and maternal preeclampsia: a critical appraisal of 1800 consecutive preeclamptic cases. J Matern Fetal Neonatal Med. 2020 Jul 6:1-7. doi: 10.1080/14767058.2020.1786516. Epub ahead of print. PMID: 32627713.

8) Robillard PY. Risk factors for early and late onset preeclampsia in women without pathological history: confirmation of the paramount effect of excessive maternal pre-pregnancy corpulence on risk for late onset preeclampsia. Integr Gyn Obstet J. 2020 , 3(3): 1-7. doi: 10.31038/IGOJ.2020331

9) Robillard PY, Boukerrou M, Bonsante F, Boumahni B, Iacobelli S. Twin chorionicity and risk of early onset preeclampsia (< 34 weeks gestation) in Reunion island. Very high risk in monozygotic twins. Eur J Obstet Gynecol Reprod Biol, 2021. *In review*.

10) Ratsiatosika AT, Razafimanantsoa E, Andriantoky VB, Ravoavison N, Andrianampanalinarivo Hery R, Boukerrou M, Iacobelli S, Robillard PY. Incidence and natural history of preeclampsia/eclampsia at the university maternity of Antananarivo, Madagascar: high prevalence of the early-onset condition. J Matern Fetal Neonatal Med. 2019 Oct;32(19):3266-3271. doi: 10.1080/14767058.2018.1462323. Epub 2018 Apr 22. PMID: 29621911.

11) Dekker GA. Risk factors for preeclampsia. Clin Obstet Gynecol. 1999 Sep;42(3):422-35. doi: 10.1097/00003081-199909000-00002. PMID: 10451762.

12) Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. Am J Obstet Gynecol. 2013 Dec;209(6):544.e1-544.e12. doi:10.1016/j.ajog.2013.08.019.

13) Townsend R, Khalil A, Premakumar Y, Allotey J, Snell KIE, Chan C, Chappell LC, Hooper R, Green M, Mol BW, Thilaganathan B, Thangaratinam S; IPPIC Network. Prediction of pre-eclampsia: review of reviews. Ultrasound Obstet Gynecol. 2019 Jul;54(1):16-27. doi: 10.1002/uog.20117. PMID: 30267475

14) Ebbing C, Rasmussen S, Skjaerven R, Irgens LM. Risk factors for recurrence of hypertensive disorders of pregnancy, a population-based cohort study. Acta Obstet Gynecol Scand. 2017 Feb;96(2):243-250. doi: 10.1111/aogs.13066. Epub 2017 Jan 6. PMID: 27874979.

15) Lučovnik M, Tul N, Verdenik I, Novak Z, Blickstein I. Risk factors for preeclampsia in twin pregnancies: a population-based matched case-control study. J Perinat Med. 2012 Feb 14;40(4):379-82. doi: 10.1515/jpm-2011-0252. PMID: 22752768.

16) Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. Am J Obstet Gynecol. 2020 Aug 21:S0002-9378(20)30873-5. doi: 10.1016/j.ajog.2020.08.045. Epub ahead of print. PMID: 32835720.

17) Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2018 Mar;218(3):287-293.e1. doi: 10.1016/j.ajog.2017.11.561. Epub 2017 Nov 11. PMID: 29138036.

18) Kalafat E, Shirazi A, Thilaganathan B, Khalil A. The role of aspirin in prevention of preeclampsia in twin pregnancies: does the dose matter? Am J Obstet Gynecol. 2020 Sep;223(3):457-458. doi: 10.1016/j.ajog.2020.03.005. Epub 2020 Mar 12. PMID: 32173447.

19) Francisco C, Wright D, Benkő Z, Syngelaki A, Nicolaides KH. Competing-risks model in screening for pre-eclampsia in twin pregnancy by maternal characteristics and medical history. Ultrasound Obstet Gynecol. 2017 Oct;50(4):501-506. doi: 10.1002/uog.17529. Epub 2017 Aug 23. PMID: 28508528.

20) Wright D, Nicolaides KH. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol. 2019 Jun;220(6):580.e1-580.e6. doi: 10.1016/j.ajog.2019.02.034. Epub 2019 Feb 21. PMID: 30797761.

21) Bicocca MJ, Mendez-Figueroa H, Chauhan SP, Sibai BM. Maternal Obesity and the Risk of Early-Onset and Late-Onset Hypertensive Disorders of Pregnancy. Obstet Gynecol. 2020 Jul;136(1):118-127. doi: 10.1097/AOG.0000000000003901. PMID: 32541276.

22) Robillard PY, Dekker G, Scioscia M, Bonsante F, Iacobelli S, Boukerrou M, Hulsey TC. Increased BMI has a linear association with late-onset preeclampsia: A population-based study. PLoS One. 2019 Oct 17;14(10):e0223888. doi: 10.1371/journal.pone.0223888. PMID: 31622409; PMCID: PMC6797165.

23) Scioscia M, Karumanchi SA, Goldman-Wohl D, Robillard PY. Endothelial dysfunction and metabolic syndrome in preeclampsia: an alternative viewpoint. J Reprod Immunol. 2015 Apr;108:42-7. doi Endothelial: 10.1016/j.jri.2015.01.009

24) Robillard PY, Dekker G, Boukerrou M, Boumahni B, Hulsey T, Scioscia M. Gestational weight gain and rate of late-onset preeclampsia: a retrospective analysis on 57 000 singleton pregnancies in Reunion Island. BMJ Open. 2020 Jul 28;10(7):e036549. doi: 10.1136/bmjopen-2019-036549. PMID: 32723741; PMCID: PMC7389512.

25) Robillard PY, Dekker GA, Boukerrou M, Boumahni B, Hulsey TC, Scioscia M. The urgent need to optimize gestational weight gain in overweight/obese women to lower maternal-fetal moribidities: a retrospective analysis on 59,000 singleton term pregnancies. Archives Women Health Care, 2020 (3) 1-9**.** DOI: 10.31038/AWHC.2020342

26) Robillard PY**.** Risk factors for early and late onset preeclampsia in women without pathological history: confirmation of the paramount effect of excessive maternal pre-pregnancy corpulence on risk for late onset preeclampsia. Integr Gyn Obstet J. 2020 , 3(3): 1-7**.** DOI: 10.31038/IGOJ.2020331

27) Robillard PY. Epidemiological evidence that severe obese women (pre-pregnancy BMI ≥40 kg/m^2) should lose weight during their pregnancy. J Matern Fetal Neonatal Med. 2021 May 24:1-6. doi: 10.1080/14767058.2021.1918666. Epub ahead of print. PMID: 34030588.

28) Kho EM, McCowan LM, North RA, Roberts CT, Chan E, Black MA, Taylor RS, Dekker GA; SCOPE Consortium. Duration of sexual relationship and its effect on preeclampsia and small for gestational age perinatal outcome. J Reprod Immunol. 2009 Oct;82(1):66-73. doi: 10.1016/j.jri.2009.04.011. Epub 2009 Aug 12. PMID: 19679359.