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Quantitative Discrimination of Small for Gestational Age (Sga) Singleton Newborns. Incidences, Risk Factors and Foetal Outcomes of the Three Major Subtypes of Sga: A 23-Year Cohort of 8,601 Singleton Sga (Out of 83,917 Births)

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Abstract

Objectives: Quantifying the different sorts of small for gestational age (SGA): constitutional SGA vs fetal growth restriction (FGR, i.e. Doppler anomalies), and verifying if the most frequent cause of FGR is associated with maternal preeclampsia.

Design: University's maternity, 23.5 year-observational population-based cohort study. All consecutive singleton pregnancies.

Main outcome Measures: Comparing risk factors between the different types of SGA's and controls (pregnancies without preeclampsia and SGA).

Results: There were 8,601 SGA/ 83,617 malformations excluded births (10.2%). Those associated with maternal preeclampsia (PES, N= 536) represented 6.2% of all SGA, those without maternal preeclampsia but diagnosed with having Doppler anomalies « vascular SGA » (VascS, N= 1,389) represented 16.1%. The remaining N= 6,676, without Doppler anomalies "constitutional SGA" (constS) comprised ¾ (77.6%) of all SGA. Singleton pregnancies without any hypertensive disease and without SGA (N= 75,316) represented the control group.

Preeclamptic mothers were on average older than controls 28.5 years vs 27.9, p=0.03. VascS and constS being younger 27.3, p<0.0001. Pre-pregnancy BMI was 25.9 kg/m² in PES vs 25.0 in controls (p< 0.0001), while it was significantly lower (24.0) in VascS and constS. In multiparas, the rate of primipaternity for the index pregnancy was much higher in PES and VascS (16.5%) compared with controls (4%) and ConstS (4.7%); OR 4.8, p< 0.0001. A history of prior preeclampsia had a similar effect in VascC and ConstS: adjOR ≈ 1.5, while a history of previous SGA had a major effect (OR 4.9). The date of delivery in the constitutional SGA group was the same than controls.

Conclusions.: First, 77%, of SGA (small for gestational age, 10% of all births) were constitutional with no special risk for the newborn. Severely ill SGA (FGR) represented only one quarter (23%) of all SGA. Second, but main findings: three quarters of these FGR belonged to pregnancies without any detectable maternal disease (preeclampsia). FGR associated with maternal preeclampsia comprized only one quarter of FGR.

Keywords: Small for gestational age; Intrauterine growth restriction; Fetal growth restriction; Preeclampsia; Gestational weight gain

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Introduction

By international consensus the 10th percentile birthweight at birth was chosen as a cutoff for small for gestational age newborns (SGA) in the 1960s [1] confirmed in 1995 by the World Health Organization published recommendations [2]. But SGA is not synonymous with fetal growth restriction (FGR), which is defined by a slowing down or even arrest in foetal growth velocity during pregnancy [3]. A constitutionally normal SGA infant must be distinguished from an FGR-SGA newborn. The former does not have an increased risk of morbidity and mortality compared to that seen in the latter [3,4]. These constitutionally normal SGA infants do not have wasted features of intrauterine malnourishment.

SGA neonates have been described to fall mainly into three groups [4]. First, constitutionally small fetuses/infants. They are identified by small size at all stages but their growth trajectory is normal following their individual centile line. No pathology is present. The constitutionally normal SGA infants can be differentiated from FGR-SGA infants by taking into consideration the height, weight, parity and ethnicity of the mother [3,4].

Second, placenta Mediated Growth Restriction: Growth is usually normal initially but slows down in utero. The diagnosis is made normally on the basis of ultrasound assessments, by at least two measurements several weeks apart. This is due to fetal growth restriction (FGR), and the newborn baby has a wasted appearance and is at a greater risk of perinatal complications. Third, non-placenta mediated growth restriction: Growth is affected by foetal factors such as a chromosomal or structural anomaly, an error in metabolism or foetal infection. Since the pioneering investigations of several authors in the 1980- 1990's [5-7] and summarized by Bamberg and Kalache [8] the paramount role of Doppler velocimetry (maternal uterine arteries, increased pulsatility index umbilical artery waveforms, decreased pulsatility index in the foetus' middle cerebral artery) became a kind of gold standard to discriminate between constitutional SGA and FGR [3,4,7-16]. In Reunion island (where access to medical care is free through the French Social Security system), women have a mean of 4 ultrasounds including Doppler velocimetry during their prenatal follow-up.

Knowing the current controversies concerning fetal growth charts [16-19], we chose to work on our country-specific charts [16]. Indeed, since 2021, having enough births in preterm pregnancies < 32 weeks gestation, local Reunion fetal growth chart were established (discriminating by sex), reproduced in Annex 1 [20]. French law forbids to collect data for ethnicities, see Annex 1. The 10th percentile was defined from this local chart.

The aim of this study is to identify and quantify the different sorts of SGA babies at birth in a practical clinical classification in non-malformed fetuses: respective weights of constitutional SGA, FGR and overall verify if the most frequent cause of FGR is associated with preeclampsia [8].

Material and Methods

From January 1st, 2001, to June 30, 2023 (23.5 years), the hospital records of all women who gave birth at the maternity of the University of South Reunion were abstracted in a standardized fashion. 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 infant hospital discharge and regularly audited by appropriately trained staff. This epidemiological perinatal data base contains information on obstetrical risk factors, description of delivery, and maternal and neonatal outcomes. For the purpose of this study, records have been validated and have been used anonymously. All pregnant women in Reunion Island as part of the French National Health Care System have their prenatal visits, biological and ultrasound examinations, at the time of the morphology scan and anthropological characteristics recorded in a maternity booklet and access to maternity care free of charge as provided by the French healthcare system, which combines freedom of medical practice with nationwide social security. Hospitals have European standards of care health care, in particular maternity services are based on scheduled appointments (8 prenatal visits and on average 4 ultrasounds).

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, and it is the only level-3 maternity (the other maternity is a private clinic, level 1). Reunion Island is a French overseas region in the Southern Indian Ocean.

Definition of exposure and outcomes

During the 23.5-year period all consecutive singleton pregnancies after 22 weeks gestation have been analysed. 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. Early onset preeclampsia is defined as preeclampsia resulting in birth before 34 weeks of gestation, late onset preeclampsia at 34 weeks and onward.

PES: SGA with diagnosed abnormal Doppler conditions on at least 2 different examinations 2 weeks apart associated with maternal diagnosis of preeclampsia or HELLP syndrome:

VascS: "VASCULAR SGA". All foetuses with diagnosed abnormal Doppler conditions and labelled "FGR" (Fetal growth restriction) i.e. confirmed abnormal growth trajectory,

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and with NO maternal preeclamptic disease. ALL coding have been made by either a midwife or a physician. We searched in all the following items the unique indication "FGR".

- Indication of labor induction (26 possible coding)
- Indication of caesarean section (35 possible coding)
- Indication of amniocentesis (15 possible coding)
- Indication of hospitalization (at the at risk clinic, 43 possible coding, or day care hospitalization and prenatal diagnosis, 45 possible coding)

ConstS: constitutional SGA at birth without all the preceding conditions (PES, VascS)

CONTROLS have been defined by all normotensive singleton pregnancies comprising newborns from the 10th to the 100th centile (SGA excluded, malformations excluded).

Primipaternity in multiparas: new paternity for the index pregnancy.

Statistical analysis

Data are presented as numbers and proportions (%) for categorical variables and as mean and standard deviation (SD) for continuous ones, as appropriate. Comparisons between groups were performed using χ^2-test and 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.

To validate the independent association of maternal age and other confounding factors on different sorts of SGA we realized a multiple regression logistic model. Variables associated with all kinds of SGA 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).

We considered the following covariates as possible confounders in this analysis with the outcome PES, VascS, constitutional -SGA: maternal age by increment of 5 years, pre-pregnancy BMII by increment of 5kg/m², smoking during pregnancy, chronic hypertension, primiparity, gestational weight gain. Among multiparas: previous preeclampsia, previous SGA and "primipaternity". We included these variables and calculated the χ^2 for trend (Mantel extension), the odds ratios for each exposure level compared with the first exposure level.

Patients and Public involvement

The South-Reunion perinatal database (since 2001) includes 264 items. It is considered as a fully medical database, datasheets are electronically completed solely by midwives, obstetricians and neonatologists. All epidemiological studies are obligatorily performed on anonymized data (French law). As such, there is no direct patient or public involvement.

Results

On the entire studied singleton-pregnancies' cohort, N= 83,917 (controls being all the women WITHOUT SGA), all kinds of SGA represented 8,601 babies (10.2%), neonatal malformations (N= 2,526, 2.8% of all singleton newborns) having been excluded. We also excluded all kinds of foetal malformations (2.8% of the cohort) including foetopathies such as CMV, rubella, parvo-virus infections, foetal alcoholic syndrome (18% of SGA in this small population of malformed fetuses).

Amongst the 8,601 SGA foetuses/newborns, those associated with maternal preeclampsia (PES, N= 536) represented 6.2% of all SGA, those without maternal preeclampsia but diagnosed with having abnormal Doppler indices during the pregnancy follow-up-« vascular SGA » (VascS, N= 1,389) represented 16.1% of the total. The remaining N= 6,676, not suspect of vascular/doppler anomalies during pregnancy, ie constitutional SGA (ConstS) comprised ¾ (77.6%) of all SGA. In this large population cohort, singleton pregnancies without any hypertensive disease and without SGA (N= 75,316) represented the control group.

Preeclamptic mothers PES were older in average than controls (28.5 years vs 27.9, p=0.03). VascS and ConstS mothers were younger than controls (27.3 years; p < 0.0001). Women with pregnancies resulting in ConstS had on average a higher parity than controls (2.2 vs 1.3, p < 0.0001), while PES and VascS had less (≈1.0, p < 0.0001). Fifty per cent of PES, VascS and ConstS were primiparae vs 36% of controls (p< 0.0001). Adolescents (< 18 years of age) were relatively protected of having PES (OR 0.67, p= 0.07), while they had larger risk for VascS and ConstS (OR 1.25, p= 0.05 and OR 1.2 p= 0.001, respectively). The rate of women over the age of 35 were similar in controls, VascS and ConstS (≈ 17%), while they were over-represented in PES (OR 1.35, p=0.009). Concerning grand-multiparas (5 children and plus), they were under-represented (≈ OR 0.7, significant) in all kinds of SGA as compared with controls. All kinds of SGA mothers were more likely to be single (≈ 42%, OR 1.2, significant) than controls (36%). There were no difference concerning the level of education between all groups (10 years of school or more ≈ 60%).

Concerning maternal BMI before pregnancy, thin women (< 18.5 kg/m²) were over-represented in VasC and

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Table 1: Maternal characteristics. Controls: women without small for gestational age newborns SGA, N= 75,316.

	Controls: singletons (SGA excluded) N= 75,316 (%)	SGA preeclamptics Vs ctrl N = 536 (%)	OR [95% CI]	P value	Vascular SGA Without PE Vs ctrl N= 1389 (%)	OR [95% CI]	P value	Constitutional SGA Vs ctrl N= 6676 (%)	OR [95% CI]	P value
Maternal age (years: mean ± sd)	27.9 ± 6.5	28.5 ± 7.1		0.03	27.3 ± 6.7		0.0005	27.3 ± 6.7		<0.0001
Gravidity ± sd	2.9 ± 1.9	2.6 ± 1.83		0.0009	2.6 ± 1.8		< 0.0001	2.7 ± 1.9		< 0.0001
Parity ± sd	1.3 ± 1.5	1.0 ± 1.4		<.0.0001	0.97 ± 1.3		< 0.0001	2.2 ± 1.5		< 0.0001
Primiparous women	27303 (35.7)	269 (50.2)	1.8 [1.5-2.1]	<.0.0001	682 (49.1)	1.7 [1.5-1.9]	< 0.0001	3067 (46.0)	1.53 [1.5-1.6]	< 0.0001
Adolescents < 18 years	2928 (3.8)	14 (2.6)	0.67 [0.4-1.1]	0.07	66 (4.8)	1.25 [1.0-1.6]	0.05	312 (4.7)	1.2 [1.1-1.4]	0.001
Age ≥ 35 years	13661 (17.9)	122 (22.8)	1.35 [1.1-1.7]	0.009	230 (16.6)	0.9 [0.8-1.06]	0.1	1096 (16.4)	0.9 [0.85-0.97]	0.01
Grand multiparas (≥ 5)	6192 (8.1)	34 (6.3)	0.77	0.08	82 (5.9)	0.72	0.001	455 (6.8)	0.84	0.001
Education 10th grade or over	44803 (61.0)	290 (57.2)	0.86 [0.72-1.02]	0.07	831 (62.6)	1.06 [0.95-1.2]	0.28	3724 (57.9)	1.06	0.1
Living single	27819 (36.6)	277 (42.4)	1.28 [1.08-1.5]	0.005	574 (41.5)	1.23 [1.1-1.37]	0.0002	2762 (41.6)	1.23 [1.17-1.3]	< 0.0001
BMI (mean ± sd)	25.0 ± 6.1	25.9 ± 6.0		0.003	24.0 ± 6.0		< 0.0001	23.9 ± 6.1		< 0.0001
Mean maternal height (m)	1.61 ± 0.07	1.59 ± 0.06		<.0.0001	1.60 ± 0.07		<.0.0001	1.59 ± 0.06		<.0.0001
Obesity ≥ 30 kg/m²	14,039 /73,620 (19.1)	116/486 (23.9)	1.33 [1.08-1.6]	< 0.0001	222/1349 (16.5)	0.85 [0.74-0.99]	0.0001	972/6419 (15.1)	0.77 [0.72-0.83]	< 0.0001
BMI < 18.5 kg/m²	14,358 /73,620 (19.5)	78/486 (16.0)	0.79 [0.62-0.99]	0.001	391/1349 (29.0)	1.66 [1.48-1.87]	<.0.0001	1840/6419 (28.7)	1.64 [1.55-1.3]	< 0.0001
Smoking	8847 (11.6)	66 (12.3)	1.05	0.34	312 (22.5)	2.2 [1.9-2.5]	< 0.0001	1306 (19.6)	1.8 [1.7-1.9]	< 0.0001
MULTIPARAS	N= 55,773	N= 347			N= 884			N= 4424		
PRIMIPATERNITY	2284 (4.0)	57 (16.4)	4.67 [3.5-6.2]	< 0.0001	144 (16.9)	4.87 [4.1-5.8]	< 0.0001	210 (4.7)	1.2 [1.04-1.4]	0.02
History of elective abortion	13560 (24.0)	77 (22.2)	0.91 [0.7-1.2]	0.21	276 (31.2)	1.4 [1.25-1.7]	0.001	1196 (27.0)	1.17 [1.1-1.26]	0.007
History of miscarriage	15425 [27.3]	117 (33.7)	1.36 [1.09-1.7]	0.007	256 [29.0)	1.09 [0.94-1.3]	0.09	1278 (28.9)	1.09 [1.01-1.16]	0.02

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ConstS, almost 1/3rd of women (29%) as compared with controls (19%), OR ≈ 1.6, p< 0.0001, and under-represented in PES (16%) OR 0.9, p=0.001. A lower maternal height (≈ 1.59m) was detected in all kinds of SGA as compared with controls (1.61m), p< 0.0001. Obesity (≥ 30 kg/m²) was over-represented in PES (23.9% vs 19%, OR 1.33, p< 0.0001) vs controls, but under-represented in VascS and ConstS vs controls (15-16% vs 19%, OR ≈ 0.8, p= 0.001). Mean BMI before pregnancy was of 25.9 kg/m² in PES vs 25.0 in controls, < 0.0001, while it was significantly lower (24.0) in VascS and ConstS. The rate of smokers was similar in PES vs controls (12%) but much higher in VascS and ConstS (20-22%, OR 2.2 and 1.8, p < 0.0001).

Concerning multiparas, the rate of primipaternity for the index pregnancy was much higher in PES and VascS (16.5%) compared with our control population of multiparas (4%), OR 4.8, p< 0.0001. This rate of primipaternity was comparable in controls (4%) vs ConstS (4.7%), although significant OR 1.2, p=0.02.

History of volunteer abortion was similar between controls and PES (22-24%, p= 0.21) and higher in VascS (31.2%) and ConstS (27%) vs controls (OR 1.4, p=0.001 and 1.17, 0.007, respectively). History of previous miscarriage was similar in VascS and ConstS (27-29%) with controls (27%) while it was slightly higher (33.7%) in PES, OR 1.36, p= 0.007.

Follow-up of all pregnancies were well done in our cohort for all pregnancies. We found no difference in the incidence of gestational diabetes between PES and controls (13%) and VascS (11.4%,) but lower in ConstS (10.9%, OR 0.83, p=0.001). Chronic hypertension was more prominent in PES (OR 6.8, p< 0.0001) and VascS in a lesser extent (OR 1.8, p< 0.0001) as compared with controls and ConstS. 'PES' women were much more hospitalized at the risk clinic during pregnancy (OR 11.5, < 0.0001), while VascS pregnancies were rather followed in the outpatient clinic (OR 9.3, both p < 0.0001). Indirect marker of premature births, steroid administration for foetal lung maturation was administered in ¼ of PES pregnancies (OR 6.4, < 0.0001), and in lesser extent in VascS (OR 2.7, p< 0.0001) but not in ConstS as compared with controls (5%). In vitro fertilization was a similar risk factor in PES and VascS pregnancies, (OR 1.9 and 1.7), but not for ConstS. The rate of amniocentesis was higher in VascS pregnancies, (OR 3.7), and to a lesser extent to PES (OR 2.3, p< 0.0001 for both), compared with ConstS and controls.

For multiparas, previous history of preeclampsia (0.8% in controls) was much higher in PES (8.3%, OR 10.4, p<0.0001), in a lesser extent in VascS (1.7%, OR 2.3, p<0.0001) but not in ConstS (OR 0.56, p< 0.0001). Previous history of SGA (0.4% in controls) was a very strong risk factor in VascS and ConstS respectively (OR 8.7 and 6.2, p< 0.0001) and in lesser extent in PES (OR 3.7, p< 0.0001, but it is of note that on this specific item, there was only one possible answer: either history of preeclampsia or history of SGA. Concerning history of previous perinatal deaths (controls 4.2%, ConstS 4.8%), PES and VascS had a higher risk (8.2% and 7.2%, OR 2.0 and 1.8, p< 0.0001 for both).

Rate of Cesarean sections (LSCS) was higher than controls in all kinds of SGA but with a strong decreasing hierarchy translated in odds ratios by OR 9 in PES, 2.7 in VascS, and 1.2 in ConstS (p< 0.0001 for all). Among these, LSCS for placental abruption was common in PES (OR 11.8, < 0.0001) but not in VascS and ConstS. The rate of induced deliveries was higher in VascS vs PES (OR 5.4 and 3.4, respectively, p< 0.0001 for both) and no significant difference in ConstS. A similar decreasing step-like hierarchy between PES/VascS/ConstS existed for mean birthweights, low-birthweights (< 2500g), very low birthweights (< 1500g), prematurity (< 37 and < 33 weeks), transfers in the neonatal department, infant respiratory distress as compared with controls. It is of note that low 3 minute APGAR scores < 7 were significantly higher in all kinds of SGA but with the same step-like hierarchy. Pregnancies resulting in ConstS did not have an increased rate of induction of labour or LSCS, also the rate of neonatal death in the first 28 days was similar to controls. However, ConstS were associated with inra uterine fetal death (OR 2.8, p< 0.0001) while much less than PES (OR 9.7, < 0.0001) or VascS (OR 3.6, < 0.0001). Noteworthy, the relatively high rate of medical termination of pregnancy due to a severe preterm FGR in VascS (OR 11.4, < 0.0001).

Table 4 evaluates the differences in maternal BMI between the 3 kinds of SGA. Overweight and all levels of obesities were over-represented in preeclamptic SGA as compared with controls. But conversely, VascS and ConstS were significantly leaner than controls at the beginning of pregnancy. Moreover, gestational weight gain at delivery was significantly lower in VascS and ConstS as compared with controls and PES.

Table 5. The multiple logistic regression model includes the 2 obligatory items having both a well-known effect on preeclampsia risk: maternal ages and maternal pre-pregnancy BMI .Concerning the risk of having SGA, maternal ages, the adjusted OR (adjOR) 1.02, are identical for PES and VascS but this difference is not significant for PES (with a quasi-nil positive coefficient, 0.02), but is significant (p=0.001) for VascS, as younger women have a decreased risk as compared with the older in VascS. For Const, maternal age has no influence. For maternal pre-pregnancy BMI, for vascS and ConstS t the higher the BMI, the lower the rate of SGA; negative coefficients (-1.01, -0.04), but not for PES. Chronic hypertension presented a very strong adjOR 3.19 for having SGA in PES, less for ConstS , adjOR 1.49, and not significant for VascS.

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Table 2: Pregnancy characteristics.

	Controls: singletons (SGA excluded) N= 75,316 (%)	SGA preeclamptics Vs ctrl N = 536 (%)	OR [95% CI]	P value	Vascular SGA Without PE Vs ctrl N= 1389 (%)	OR [95% CI]	P value	Constitutional SGA Vs ctrl N= 6676 (%)	OR [95% CI]	P value
Number of prenatal consultations (mean ± sd)	8.7 ± 2.7	7.9 ± 3.0		< 0.0001	8.8 ± 2.7		0.22	8.7 ± 2.8		0.07
Number of ultrasounds	4.4 ±1.5	5.0 ±2.0		< 0.0001	5.7 ± 2.1		< 0.0001	4.5 ±1.7		0.0001
Timing 1st echography (weeks: mean ± sd)	11.3 ± 4.0	11.3 ± 4.0		0.79	11.4 ± 4.0		0.66	11.5 ± 4.1		0.0001
Gestational diabetes	9815 (13.0)	73 (13.7)	1.07	0.09	156 (11.4)	0.87	0.08	724 (10.9)	0.83 [0.77-0.90]	0.001
Chronic hypertension	1014 (1.3)	45 (8.4)	6.8 [5.0-9.3]	< 0.0001	33 (2.4)	1.8 [1.27-2.6]	< 0.0001	106 (1.6)	1.2 [0.98-1.5]	0.09
Hospitalizations in at risk clinic	10203 (13.3)	343 (64.0)	11.5 [9.7-13.8]	< 0.0001	480 (34.6)	3.5 [3.1-3.9]	< 0.0001	807 (12.1)	0.92 [0.85-0.99]	0.01
Follow-up in outpatient clinic	7790 (10.6)	81 (15.7)	1.6 [1.2-2.0]	< 0.0001	712 (52.3)	9.3 [8.3-10.3]	< 0.0001	581 (9.1)	0.85 [0.78-0.9]	< 0.0001
Steroids for fœtal lung maturation	3758 (4.9)	133 (24.9)	6.4 [5.2-7.8]	< 0.0001	170 (12.5)	2.7 [2.3-3.2]	< 0.0001	224 (3.4)	0.67 [0.6-0.8]	< 0.0001
In vitro fecundation	525 (0.7)	7 (1.3)	1.9 [0.9-4.0]	0.09	16 (1.2)	1.7 [1.03-2.8]	0.03	45 (0.7)	0.99	0.19
Amniocentesis	3265 (4.3)	50 (9.3)	2.3 [1.7-3.0]	< 0.0001	202 (14.5)	3.7 [3.2-4.3]	< 0.0001	266 (4.0)	0.91	0.88
MULTIPARAS	**N= 55,773**	**N= 347**			**N= 884**			**N= 4424**		
History of preeclampsia	639 (0.8)	44 (8.3)	10.4 [7.6-14.4]	< 0.0001	23 (1.7)	2.3 [1.5-3.5]	< 0.0001	65 (0.01)	0.56 [0.46-0.68]	< 0.0001
History of previous SGA	310 (0.4)	8 (1.5)	3.7 [1.5-4.4]	0.001	41 (3.0)	8.7 [6.2-12.1]	< 0.0001	149 (2.2)	6.2 [5.1-7.6]	< 0.0001
History perinatal deaths	2334 (4.2)	28 (8.2)	2 [1.4-3.0]	0.0003	62 (7.2)	1.8 [1.36-2.3]	< 0.0001	207 (4.8)	1.1 [0.99-1.3]	0.07

Table 3: Some delivery characteristics and neonatal characteristics.

	Controls: singletons (SGA excluded) N= 74,791 (%)	SGA preeclamptics Vs ctrl N= 497	OR [95% CI]	P value	Vascular SGA Without PE Vs ctrl N= 1352 (%)	OR [95% CI]	P value	Constitutional SGA Vs ctrl N= 6562 (%)	OR [95% CI]	P value
Rate of LSCS (%)	11,363 (15.0)	313 (63.0)	9 [8.1-11.]	< 0.0001	432 (32.0)	2.7 [2.4-3]	< 0.0001	1147 (17.5)	1.2 [1.1-1.3]	< 0.0001
Placental abruption	157 (0.20)	12 (2.4)	11.8 [6.2-20.7]	< 0.0001	1 (0.07)	0.2 [0.48-0.96]	< 0.0001*	0 (0)		< 0.0001
Induced deliveries (%)	15551 (20.5)	233 (46.9)	3.4 [3.2-4]	< 0.0001	777 (57.5)	5.4 [4.8-6]	< 0.0001	1322 (20.9)	1.05 [0.99-1.1]	0.08
Fetal sex Girl	37,028 (50.4)	257 (51.7)			724 (53.6)			3373 (51.4)		
Delivery term (weeks): mean ± sd	38.5 ± 2.0	35.2 ± 6.7		< 0.0001	37.4 ± 2.3			38.9 ± 1.4		< 0.0001
Mean Birth weight (g)	3176 ± 500	1808 ± 627		< 0.0001	2146 ± 500		< 0.0001	2512 ± 268		< 0.0001
Low birth weight <2500g	4489 (5.9)	428 (86.1)	98 [76-127]	< 0.0001	1087 (80.4)	65 [57-75]	< 0.0001	2586 (39.4)	10 [9.-11]	< 0.0001
Very low birth weight <1500gr	864 (1.1)	145 (29.2)	35.8 [29-44]	< 0.0001	127 (9.4)	9.1 [7.5-11]	< 0.0001	42 (0.6)	0.57 [0.41-0.77]	< 0.0001
Prematurity <37 weeks of gestation	6456 (8.5)	270 (54.3)	12.8 [10.7-15.3]	< 0.0001	289 (21.4)	2.9 [2.6-3.4]	< 0.0001	237 (3.6)	0.4 [0.34-0.45]	< 0.0001
Prematurity <33 weeks	1347 (1.8)	101 (20.3)	14.1 [11.3-17.7]	< 0.0001	63 (4.7)	2.7 [2.1-3.5]	< 0.0001	22 (0.3)	0.9 [0.12-0.28]	< 0.0001
Transfer in neonatal department	5263 (6.9)	314 (63.2)	23 [19-27]	< 0.0001	547 (40.5)	9.2 [8.2-10.3]	< 0.0001	795 (12.1)	4.9 [1.7-2.0]	< 0.0001
Infant respiratory distress syndrome	551 (0.7)	41 (8.2)	12.3 [8.8-17.1]	< 0.0001	25 (1.8)	2.6 [1.7-3.9]	< 0.0001	12 (0.2)	0.25 [0.14-0.45]	< 0.0001
3-min Apgar score < 7	3721 (4.9)	104 (21.1)	5.2 [4.2-6.5]	< 0.0001	1.6 (7.9)	1.7 [1.4-2.0]	< 0.0001	4.6 (6.2)	1.3 [1.16-1.44]	0.001
LIVEBORN AND FETAL DEATHS	**N= 75,316 (%)**	**N = 536 (%)**			**N= 1389 (%)**			**N= 6676 (%)**		
Outcome :										
In utero fetal death	430 (0.6)	28 (5.2)	9.7 [6-14]	< 0.0001	27 (1.9)	3.6 [2.4-5]	< 0.0001	101 (1.5)	2.8 [2-3.4]	< 0.0001
Medical termination	48 (0.06)	11 (2.1)	33 [17-64]	< 0.0001	10 (0.7)	11.4 [6-22]	< 0.0001	9 (0.13)	2 [0.96-4.3]	0.08 §
*** death <28 days**	283 (0.4)	22 (4.4)	12.4 [8-19]	< 0.0001	9 (0.7)	1.7 [0.78-3.3]	0.08 §	12 (0.2	0.5 [0.3-0.9]	< 0.0001

* Mantel Haenszel test § Fisher exact test

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Table 4: Maternal BMI and gestational weight gain.

	Controls: singletons (SGA excluded) N= 72,530 (%)	SGA preeclamptics Vs ctrl N = 486 (%)	OR [95% CI]	P value	Vascular SGA Without PE Vs ctrl N= 1349 (%)	OR [95% CI]	P value	Constitutional SGA Vs ctrl N=6419 (%)	OR [95% CI]	P value
Mean maternal height (m)	1.61 ± 0.07	1.59 ± 0.06		<.0.0001	1.60 ± 0.07		<.0.0001	1.59 ± 0.06		<.0.0001
BMI (mean ± sd)	25.0 ± 6.1	25.9 ± 6.0		0.003	24.0 ± 6.0		< 0.0001	23.9 ± 6.1		< 0.0001
Delivery term (weeks): mean ± sd	38.5 ± 2.0	35.2 ± 6.7		< 0.0001	37.4 ± 2.3			38.9 ± 1.4		< 0.0001
Weight gain, kg at delivery (mean ± sd)	11.9 ± 6.4	11.6 ± 6.2		0.36	9.9 ± 6.0		< 0.0001	10.3 ± 6.1		< 0.0001
Adjusted Weight gain at 38.5 weeks gestation, kg	11.9 ± 6.4	12.7 ± 6.2		< 0.0001	10.2 ± 6.0		< 0.0001	10.2 ± 6.1		< 0.0001
10-14.9 kg/m²	253 (0.3)	3 (0.6)	49.8.% vs 59.1%		10 (0.7)	64.9% vs 59.1%		62 (1.0)	66.2% vs 59.1%	
15-19.9 kg/m²	14,032 (19.3)	75 (15.4)	**0.68**		381 (28.2)	**1.28**		1778 (27.7)	**1.35**	
20-24.9 kg/m²	28,629 (39.5)	164 (33.7)	**[0.6-0.8]**		485 (36.0)	**[1.1-1.4]**	**< 0.0001**	2408 (37.5) 1199 (18.7)	**[1.28-1.4]**	
25-29.9 kg/m²	16,022 (22.1)	128 (26.3)		**<.0.0001**	251 (18.6)			587 (9.1)		**< 0.0001**
30-34.9 kg/m²	8113 (11.2)	79 (16.3)	50.2% vs 40.9%		143 (10.6)	35.1% vs		249 (3.9)	33.8% vs 40.9%	
35-39.9 kg/m²	3583 (4.9)	30 (6.2)	**1.46**	**<.0.0001**	58 (4.3)	0.409		136 (2.1)	**0.74**	**< 0.0001**
Over 40 kg/m²	1898 (2.5)	7 (1.4)	**[1.2-1.6]**		21 (1.6)	**0.78 [0.7-0.87]**	**< 0.0001**		**[0.7-0.8]**	

Table 5: Multiple logistic model with different outcomes 1) SGA associated with preeclampsia PES, N= 536 2) Vascular SGA (abnormal Doppler without any maternal disease, N=1389, 3) Constitutional SGA, "ConstS", N= 6676.

	Outcome PES Preeclamptic SGA				Outcome VascS Vascular SGA Without maternal PE				Outcome ConstS Constitutional SGA			
	Coefficient	OR	95% CI	P	Coefficient	OR	95% CI	P	Coefficient	OR	95% CI	P
Maternal Age (increment of 5 years of age)	0.015	**1.02**	[0.99-1.04]	0.23	0.02	**1.02**	[1.008-1.03]	0.001	0.0004	**1**	[0.99-1.0	0.9
Pre-pregnancy BMI (increment of 5 kg/m²)	-1.012	**0.99**	[0.96-1.01]	0.31	-0.04	**0.95**	[0.94-0.97]	< 0.0001	-0.04	**0.96**	[0.95-0.97]	< 0.0001
Chronic hypertension	1.16	**3.19**	[1.62-6.25]	0.0008	0.23	**1.27**	[0.72-2.2]	0.41	0.4	**1.49**	[1.15-1.9]	0.002
Primiparity	1.21	**3.36**	[2.3-4.8]	< 0.0001	1.08	**2.9**	[2.1-3.6]	< 0.0001	0.39	**1.48**	{1.3-1.65]	< 0.0001
New father for the index pregnancy §	0.92	**2.52**	[1.58-4.0]	0.0001	0.97	**2.6**	[2.1-3.3]	< 0.0001	0.08	**1.08**	[0.91-1.3]	0.34
Previous preeclampsia §	1.13	**3.1**	[1.6-5.9]	0.0007	0.43	**1.5**	[0.91-2.6]	0.1	0.31	**1.37**	[1.04-1.8]	0.02
Previous SGA §	0.95	**2.6**	[0.95-7.1]	0.06	1.3	**4.9**	[3.3-7.3]	< 0.0001	1.6	**4.9**	[3.8-6.2]	< 0.0001
Gestational weight gain	0.016	**1.01**	[0.99-1.04]	0.18	-0.05	**0.94**	[0.93-0.96]	< 0.0001	-0.02	**0.95**	[0.94-0.95]	< 0.0001
Smoking during pregnancy	0.16	**1.18**	[0.77-1.8]	0.45	0.85	**2.3**	[1.9-2.8]	< 0.0001	0.7	**2.03**	[1.84-2.2]	< 0.0001

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Primiparity is a strong risk factor for PES and VascS , but with a lower impact in ConstS (≈ adjOR 3 vs 1.49). primipaternity for the index pregnancy has a similar impact (adjOR ≈3, p < 0.0001) for PES and VascS, but none in ConstS. Multiparas, who had previous preeclampsia or SGA, have a similar effect in VascS and ConstS (adjOR ≈ 1.5) for the history of preeclampsia, but a major effect for the history of previous SGA (OR 4.9). Previous preeclampsia is a major risk factor for PES (adjOR 3.1), while previous SGA had less effect (adjOR 2.6, NS) for PES. Gestational weight gain has negative coefficient (-0.05, -0.02) for VascS and ConstS: more you gain weight, less you have SGA, this effect is not significant in PES. Smoking during pregnancy has a strong impact in VascS (adjOR 2.3), and ConstS adjOR 2.0, p< 0.0001), but not significant in PES.

Figure 1 synthetizes our cohort: Our results may be summarized in terms of quarters: Three quarters of SGA (we coined "ConstS" in this study) may be qualified as "constitutional SGA" rather linked with Low maternal BMI and ethnicity. The remaining quarter is obviously associated with "Doppler anomalies" detected during antenatal care, as surrogate markers of feto-placental insufficiency and as such FGR. Inside this minority of cases, three quarters of cases are VascS i.e. only the foetus is affected without any harm to the mother. Only one quarter of these "poor Doppler pregnancies" are associated with a harmful maternal disease presenting as global endothelial dysfunction/inflammation (proteinuria/glomeruloendotheliosis, HELLP, eclampsia..). It is noteworthy that the constitutional SGA curve is exactly similar to that of controls (women with normal pregnancy and without SGA at birth). Those constitutional SGA deliver exactly like controls, these newborns share exactly the same patterns except that they are of simply "smaller".

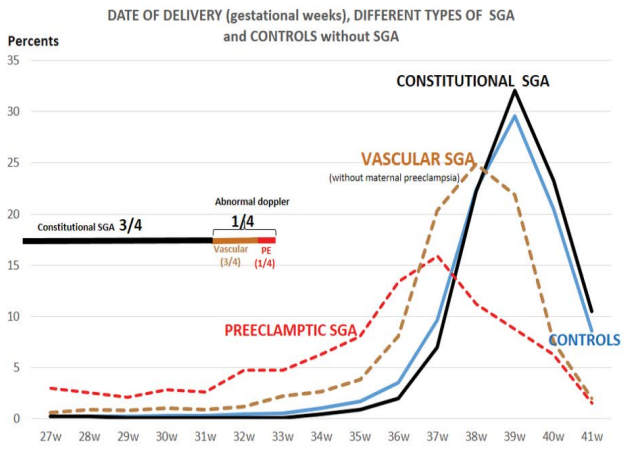

Figure 1: Date of delivery (gestational weeks), different types of SGA: preclampsia associated PES (N= 536), Vascular SGA without maternal preeclampsia VascS (N= 1389), Constitutionnal ConstS (N= 6676), and controls without SGA (N= 75,316).

Discussion

The alleged universal shape of human births worldwide is that lean women give more likely birth to 'lean' babies, and therefore SGA < 10th percentile of a neonatal population (and very few LGA), while overweight or obese women have a natural tendency to give birth to heavier babies than normal (and very few SGA). This paradigm is deeply embedded in physicians', midwives' and scientist's minds and even much more in the general population. One of the findings of this study confirms that constitutional SGAs indeed represent ¾ (77%) of these 'lean babies'. Here, we may have possible action through possibly defining optimal gestational weight gains in underweight mothers [21,22], see the end of this discussion.

However, the main findings of this study (very surprising for us) is that the vast majority (three quarters) of these FGR cases (bad vascular/nutritional exchanges between the mother and the fetus mainly in the 3rd trimester of pregnancy) with mostly underlying superficial transformation of the spiral arteries, are indeed foetuses where the mothers do NOT manifest any maternal syndrome (preeclampsia). This highly contradicts some typical textbook knowledge such as « the most frequent cause of FGR in a normally formed fetus is maternal vascular disease in association with preeclampsia » [8]. In terms of evolutionary medicine, this highly preponderant absence of any maternal disease in these very harmful situations for the fetuses, suggests that the human species developed a tremendous safety mechanism to thwart the terrible maternal preeclamptic/eclamptic complications. It might also have an escape mechanism by the fact that many FGR babies are born < 37 weeks (Indeed birthweight in preterm babies is mostlty in the lower birthweight centiles with placental lesions of maternal vascular malperfusion). If all these foetuses had also induced a maternal preeclamptic disease, the rate of preeclampsia would be have been of 10-15% (and eclampsia 3-4% !!). At these rates, our species would probably have not survived (could it have happened in Neanderthals?).

It is of interest to compare clinical risk factors between Vascular FGR (VascS) and Preeclamptic ones (PES) and as they both share documented doppler anomalies all along their pregnancy follow-up. Synthetizing results of Tables 1 to 4, we notice that we are facing on one hand strong common risk factors with PES, and on the other many common specificities with constitutional SGA (ConstS) as compared with controls. First, for the common risk factors with PES we detect. Primiparity (50% and 49% vs 35.7% in controls), mean parity (1.0 and 0.97 vs 1.3 in controls), and, in multiparas, exactly the same rate of primipaternities for the index pregnancy (16.5% and 16.9% vs 4.0% in controls). These common patterns suggest a same frame between VascS and PES and, to date with the already well-known epidemiological risk

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factors for early onset preeclampsia occurring at < 34 weeks and disease of first couples' pregnancies: the immunological approach (the shallow cytotrophoblastic implantation being somewhere considered as a partial « hemi-graft rejection ») [23].

Second, and on the other hand, although VascS being considered as 'surrogate FGR' (pathological Doppler) there are two main common characteristics between VascS and constitutional SGA rather associated with 'physiological' maternal issues: younger maternal ages and lower BMI. For maternal age, 27.3 years vs 28.5 PES and 27.5 controls. For BMI, 24.0 kg/m² vs 25.9 PES and 25.0 controls, p< 0.0001. Table 4 shows that the women giving birth to these 2 types of SGA have actually lower rates of overweight or obesities compared with, controls (OR = 0.78, p < 0.0001), while for these categories the OR for PES is of 1.46, p < 0.0001. They present also the same rate of adolescent pregnancies higher than controls and PES (4.8% vs 3.8% controls and 2.6% PES) and women over 35 years of age (16.6% vs 17.9 controls and 22.8% PES). While being difficult to interpret (older dates of deliveries in ConstS), VascS and ConstS pregnancies share a similar gestational weight gain (10.2 kg), much less than controls 11.9 kg (and PES 12.7 kg).

The particular case of smoking (Table 1). Smoking is well-known to be associated with SGA, confirmed in our cohort with 19.6% of women smoking in ConstS vs 11.6% controls (OR 1.8, p< 0.0001). But, also, in the late 1960's several research groups demonstrated that while smoking is associated with lower birthweight it is associated with a lower rate of preeclampsia (30% decrease in smokers) [24-26]. The incidence of smokers in even higher in VascS: 22.5% vs 11.6 controls (OR 2.2, p< 0.0001). This suggests that tobacco use, besides younger maternal ages and lower BMI in VascS, is also an important component as 'protector' to avoid the maternal preeclamptic disease. In an apparent paradox the rate of smokers in preeclamptic SGA, PES, is similar to controls 12.3% vs 11.6%, NS. However, since this study focusses on SGA pregnancies, the aforementioned 30% lower rate of preeclampsia primarily relates to late-onset preeclampsia (typically mostly resulting in normal birthweights [27]).

Finally, it is noteworthy (Table 3) that the only bad neonatal outcome in constitutional SGA is the rate of in utero fœtal death as compared with controls: 1.5% vs 0.6%, OR 2.8, p < 0.0001, while lower than VascS or PES (1.9% and 5.2% respectively. Constitutional SGA would not have been recognized, ie. mostly allowed to go to term and even post-term while PES and VascS are typically diagnosed and delivered earlier, see Figure 1.

The strength of our study is the capturing of all perinatal outcomes in our maternity, European standard of care. With 4,300 births per year, the university maternity, level 3, represents 82% of all births in the south of the island. The data in this large cohort are homogeneous as they were collected in a single center (lower variability) and not based on national birth registers but directly from medical records (avoiding inadequate codes). A weakness of this study is that primipaternity was obviously underestimated as this issue has been added in our database and then prospectively recorded only since 2018. Since then, we have approximately 190 multiparas per year having a new male partner (5.6% of our multiparas). New paternity ("primipaternity) was recalled during the period 2001-2017 on free commentaries possible in our database, and then probably under-represented. We may assume that the retrieved free commentaries on paternity have been biased towards the risk of preeclampsia (as primipaternity is known to be associated with this disease). However, we feel that this possible over-representation of preeclamptic pregnancies may be a "good bias" as, controlling for preeclampsia, primipaternity remains a strong independent risk factor for FGR.

Another possible weakness is that for Vascular SGA without maternal preeclamptic disease, VascS, we do not have in our perinatal database a specific item "pathological Dopplers". Therefore, we collected the indication "Foetal growth restriction" for different items (indication of caesarean section, induced deliveries, amniocentesis, hospitalizations….., see methods). It may have had the well-known confusion between SGA and FGR. But, on the other hand, all coding for these items have been chosen by medical health workers (midwives, physicians) who knew the meaning of indications for the selected items.

We worked on a country-specific chart [16,20], see Annex 1, and not on a customized one (e.g. maternal height, weight, parity and ethnicity + fetal sex). In our multiethnic society in the island of Reunion (Euopeans ≈ 10%, Africans ≈ 20%, Asian-Indians ≈ 15%, Chinese ≈ 2-5%, all the rest being « mixed » people. Additionally, the French law forbids absolutely to record data on religions, political opinions and ethnicities in any scientific database. But we feel that in our conditions, our results may be as reliable as possible to address the aims of this study.

Some 77 % of the SGA neonates were Constitutional ones. We may have a possible counter-action to reduce the rate of ConstS: counselling these lean women at the beginning of pregnancy about their individualized an optimal gestational weight gain, OptGWG, to achieve at term (following the previously published formula in 2018 in Heliyon (Open source of the Lancet): OptGWG (kg) = -1.2 ppBMI (kg/m²) + 42, [21]. Most of these neonates were born to women with a low BMI, these women only achieving a mean GWG around10 kg, see Table 4. Indeed referring to the aforementioned calculation of optGWG [22] based on individual BMI required to achieve a normal birthweight distribution, should have been in the 15-20 kg range.

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Conclusion

Only one quarter of our SGA could be considered as problematic (Fetal Growth restriction) associated with "Placental Doppler anomalies". Inside this minority of cases, the main findings is that in three quarter of cases only the foetus is affected without any harm to the mother. Only one quarter of these "poor doppler pregnancies" are associated with a very dangerous maternal disease presenting a global vascular inflammation (proteinuria-glomeruloendotheliosis, HELLP, eclampsia..). We hope that other teams could quickly confirm these important data. The possible consequences are 1) the human species found in evolution a very bright adaptation against the harmful preeclampsia 2) biological research (genetics, multiomic screening….) could concentrate on comparisons between the ¾ of "vascular" FGR without maternal preeclampsia and preeclamptic FGRs, trying to find the biological patterns which triggers the onset of the maternal disease.

In fact, three quarters of SGA at birth in humans are simply constitutional SGA, belonging to a Maternal-Fetal Body Size Association, and not due to any defect of trophoblast implantation. There, we may have a simple solution by a long 8-month prenatal follow-up concerning optimal gestational weight gain [21,22].

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Annex 1:

XI - COURBE 10ÈME 90ÈME PERCENTILE RÉUNION

PAR SEMAINES D'AMÉNORRHÉE ET PAR SEXE FOETAL

Base de données de 87 516 grossesses. PY Robillard CHU Sud-Réunion, 2022

Croissance fœtale. Réunion, 2022

N = 40 803 garçons et 39 985 filles

(Grossesses singletons, Décés foetaux exclus (MFIU, ITG), Malformations foetales exclues)

	5è Percentile	5è percentile	10è percentile	10è percentile	50è percentile	50è percentile	90è percentile	90è percentile
SA	Garçons	Filles	Garçons	Filles	Garçons	Filles	Garçons	Filles
23	478	405	522	440	600	550	702	685
24	550	459	580	486	680	655	819	790
25	550	460	650	558	800	747	946	880
26	580	500	676	584	882	795	1052	1000
27	654	540	720	630	1000	890	1200	1130
28	746	640	790	720	1100	1010	1373	1258
29	885	704	910	820	1230	1160	1530	1430
30	970	815	993	890	1392	1280	1730	1673
31SA	1084	995	1191	1070	1600	1466	1918	1860
32	1233	1106	1359	1201	1765	1642	2162	2107
33	1356	1304	1530	1430	1970	1850	2370	2280
34	1569	1461	1740	1605	2240	2090	2670	2560
35 SA	1810	1710	1960	1859	2430	2340	2920	2860
36	2019	1922	2160	2060	2680	2560	3220	3125
37	2240	2120	2390	2280	2900	2800	3474	3350
38	2480	2360	2620	2500	3100	2980	3650	3520
39	2620	2540	2760	2670	3260	3130	3800	3650
40	2760	2650	2890	2780	3380	3250	3920	3780
41	2840	2730	2980	2880	3490	3340	4040	3890

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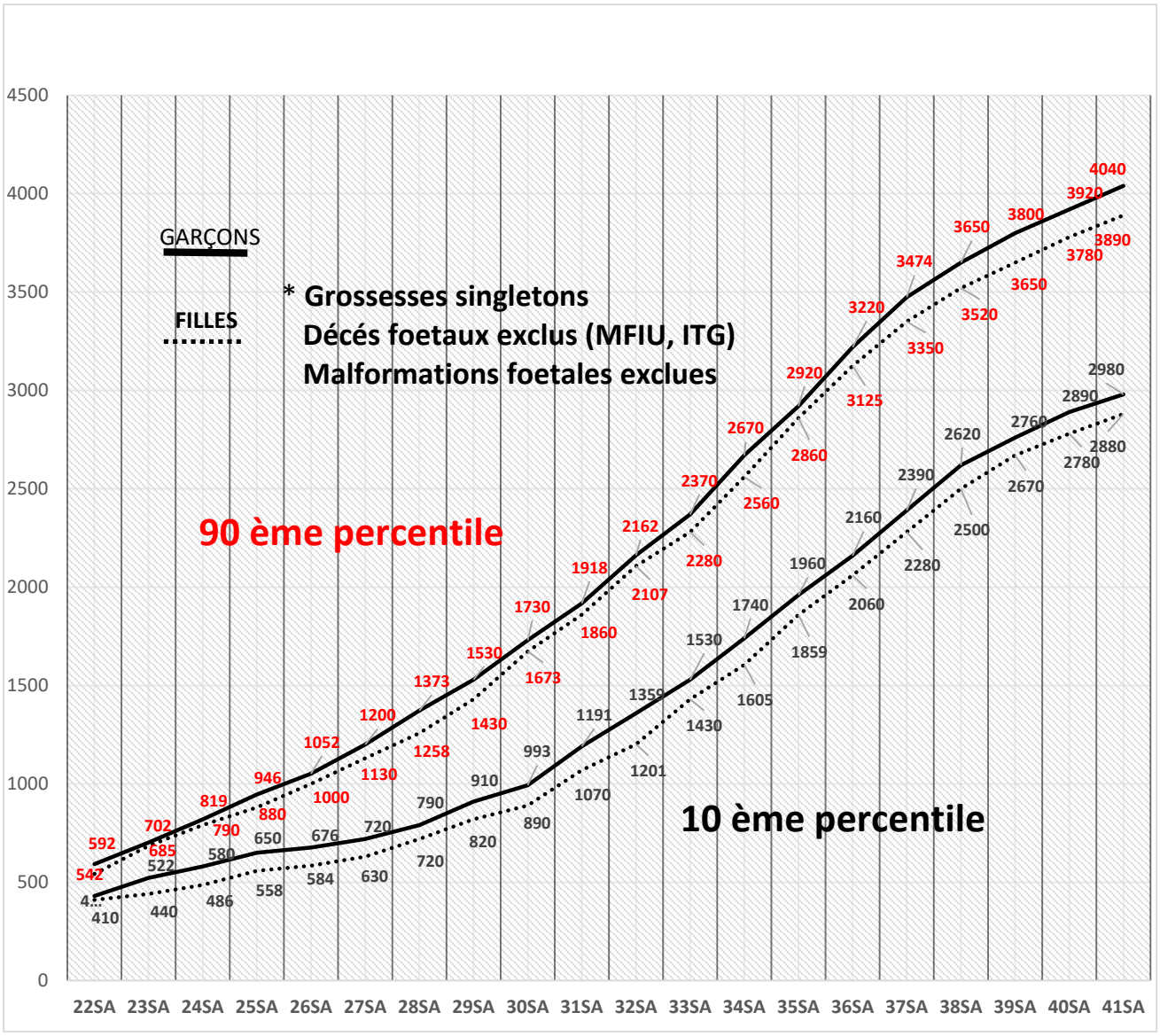
COURBE DE CROISSANCE FOETALE REUNION, 2022



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