Eur J Pediatr (2006) 165: 717–725
DOI 10.1007/s00431-005-0045-4

ORIGINAL PAPER

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Identification of newborns with Fetal Growth Restriction (FGR) in weight and/or length based on constitutional growth potential

Received: 12 July 2005 / Accepted: 28 October 2005 / Published online: 12 July 2006

Abstract This study was carried out to build statistical models for defining FGR (Fetal Growth Restriction) in weight and/or length after taking growth potential of an infant into account. From a cohort of pregnant women having given birth to 47,733 infants in 141 French maternity units, two statistical models gave individualized limits of birth weight and birth length (based on the 5th centile) below which, after adjustment for its individual growth potential, a newborn must be considered as FGR in weight and/or in length. A sample of 906 infants had measures taken of cord blood growth factors (IGF1, IGFBP3). The FGR_W definition (weight<5th centile for growth potential) permitted the identification of infants who presented rates of maternal hypertension (13.6%) and of Apgar score at 5 min<6 (2.9%) higher than in the classical group SGA_W (weight<5th centile for sex and gestational age) (9.6% and 2.2% respectively). By combining FGR_W and SGA_W, a subgroup of infants, not currently recognized as SGA, presented very high rates of maternal hypertension (19.9%) and of low Apgar score (3.9%). Conversely a subgroup of infants, currently recognized as SGA_W, had rates as low as in the normal infants group, and had to be considered as "constitutionally small" (that is to say 24% of the SGA_W). Combining FGR_W and FGR_L (length<5th centile of growth potential), 7.6% of infants appeared growth-restricted, and 1.8% appeared constitutionally small in weight and/or in length. The FGR_W–FGR_L infants showed the lowest mean values of IGF1 (126.2 ± 3.2) and IGFBP3 (0.86 ± 0.03). These new definitions of FGR_W and FGR_L could help to better identify infants at birth requiring neonatal care, and monitoring of growth catch-up and neurodevelopmental outcome.

Keywords FGR · Constitutional growth potential · Growth factors · Gravidic hypertension · Long term outcome

This study was funded by grants from INSERM-IDS and Novo-Nordisk Laboratory.

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Abbreviations SGA: small for gestational age · SGA_W: SGA in weight · SGA_L: SGA in length · IUGR: intrauterine growth retardation · FGR: fetal growth restriction · FGR_W: FGR in weight · N_W: normal weight · Cs_W: constitutionally small in weight · $FGR_{W\ I}$: FGR_W-type I · $FGR_{W\ II}$: FGR_W-type II · FGR_L: FGR in length · N_L: normal length · Cs_L: constitutionally small in length · $FGR_{L\ I}$: FGR_L-type I · $FGR_{L\ II}$: FGR_L-type II

Introduction

Intra-uterine growth retardation has considerable impact on health status either at birth (fetal distress, premature delivery, neonatal morbidity), during childhood (abnormal neurodevelopmental outcome, lack of catch-up growth possibly requiring growth hormone therapy), or at adult age (fetal origin of cardiovascular and endocrinological diseases) [1, 4, 6, 8–10, 15]. According to the International SGA Advisory Board Panel, the term Small for Gestational Age (SGA) refers to an abnormal size of an infant at birth, in weight and/or in length, while the term Intrauterine Growth Retardation (IUGR) suggests a diminished growth velocity in the fetus [15]. Various statistical limits are used for defining SGA infants, based on the 3rd, the 5th, the 10th centile or on the m-2SD value of growth curves according to sex and gestational age [3, 15, 18, 25]. Furthermore, the term Fetal Growth Restriction (FGR) was introduced for dealing with newborns that had not achieved their constitutional growth potential *in utero* [7]. Due to the lack of specific definition until now, FGR refers usually to the same limits as SGA [2].

Taking the constitutional growth potential into account is not a new goal, demographic factors such as maternal age, parity, race, height and weight being recognized as influencing the size at birth and in adulthood [3, 11, 19]. The classical method, consisting of dividing the population into subgroups according to fetal or maternal characteristics, raises an evident problem of sample size [19]. We previously proposed a method for adjusting birth weight limits to maternal constitutional determinants, and were able to differentiate constitutionally-small infants from those who had an impaired growth [17]. Other authors, such as Sanderson et al., Wilcox et al. or Kramer et al., also proposed methods based on statistical models of birth weight [13, 20, 23]. However, in these approaches only birth weight was taken into consideration.

The purpose of this paper is: (1) to elaborate a new statistical model for defining FGR based on the estimation of individualized birth weight or birth length limits of an infant, taking its constitutional growth potential into account, (2) to describe clinical and biological characteristics of infants according to this new definition after taking birth weight and birth length separately into account, and (3) to describe clinical and biological characteristics of infants according to this new definition after taking birth weight and birth length simultaneously into account.

Subjects and methods

Population

The cohort comprised 57,198 pregnant women who had given birth to 58,364 infants between 1999 and 2001, in 141 maternity units located in different regions of France, well distributed across the country, and participating in the French AUDIPOG Sentinel Network (AUDIPOG: Association of Users of Computerized Medical Records in Paediatrics, Obstetrics and Gynaecology). Maternal and neonatal data, routinely collected and computerized from the beginning of pregnancy to delivery, were as follows: maternal age, height, pre-pregnancy weight, ethnic origin, tobacco consumption, pathology during pregnancy, parity, sex, gestational age, birth weight, birth length, Apgar score at 1 and 5 min and neonatal transfer. Gestational age was determined from the 1st day of LMP associated with the result of the first systematic ultrasonographic examination (before 12 weeks of pregnancy). After exclusion of foetuses deceased in utero and of records where the main maternal data were missing, the final cohort comprised 47,733 infants including 1,640 twins, 82 triplets and 48 quadruplets born from 46,896 women. Sex, gestational age and birth weight were known for the total cohort and birth length for 43,654 infants. From this cohort, a sub-cohort was composed of 5,186 infants born in Lyon. Among them, 4,344 infants had cord blood samples taken at birth in order to measure growth factors (IGF1, IGFBP3). The infants were then followed up until they were discharged from maternity units.

Statistical method for modelling individual intra-uterine growth in weight and in length

The total cohort was used to model the expected birth weight and birth length of an infant after taking its individual constitutional growth potential into account. Among determinants of fetal growth, we distinguished those that might physiologically influence fetal growth (maternal age, ethnic origin, height and pre-pregnancy weight, parity, sex and gestational age) and those that might lead to impaired fetal growth (tobacco, alcohol/toxic consumption, hypertension …). The statistical method used to construct the birth weight model was a backwards stepwise multiple regression analysis, including the logarithm of birth weight (LnBW) as a dependent variable, and power functions of maternal age, ethnic origin, height, pre-pregnancy weight, parity, sex and gestational age as independent variables.

Classification of newborns as FGR_W or FGR_L according to their constitutional growth potential

In a first step, infants were classified as SGA in weight (SGA_W) or SGA in length (SGA_L) according to the 5th centile to the French AUDIPOG curves [18]. In a second

step, they were classified as FGR in weight (FGR_W) or FGR in length (FGR_L), according to the above models. Considering both new and classical definitions identifying FGR_W and SGA_W, four subgroups of infants were isolated according to their birth weight: (1) no FGR_W and no SGA_W infants, called "normal weighted" (N_W); (2) no FGR_W infants, classically and wrongly classified SGA, which according to their low individual growth potential should be considered as small, called "constitutionally small in weight" (Cs_W); (3) FGR_W infants, classically classified SGA, called "FGR_W-type I" (FGR_{WI}); and (4) FGR_W infants, classically and wrongly classified no SGA, but which should be considered as growth-restricted according to their strong individual growth potential, called "FGR_W-type II" (FGR_{WII}).

In the same way, considering birth length, 4 other subgroups of infants were isolated: (1) no FGR_L and no SGA_L infants, called "normal length" (N_L); (2) "constitutionally small in length" infants (Cs_L); (3) "FGR_L-type I" infants ($FGR_{L\ I}$); and (4) "FGR_L-type II" infants ($FGR_{L\ II}$).

Clinical criteria

Because maternal hypertension during pregnancy and low Apgar score at 5 min are commonly seen in FGR infants suffering from impaired fetal growth, these two parameters were chosen for validating our models. 1747 women out of 46,896 (3.7%) presented maternal hypertension, and 541 newborn out of 47,733 (1.1%) had an Apgar score at 5 min ≤ 6.

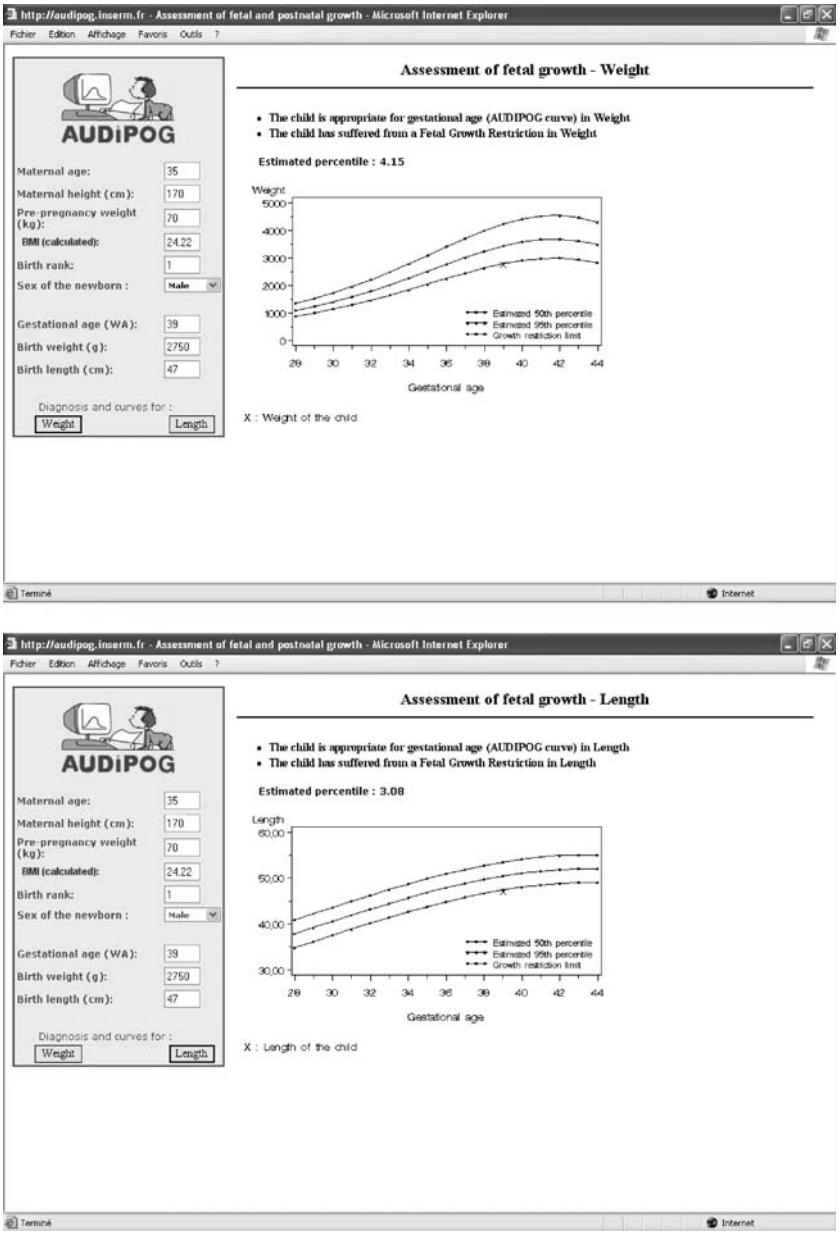

Fig. 1 Classification of an infant as SGA (small for gestational age) and/or FGR (fetal growth restriction) after taking into account constitutional growth potential on the AUDIPOG website (http://audipog.inserm.fr/) Example: a child born at 39 weeks gestational age, weighing 2,750 g, measuring 47 cm, from a mother weighting 70 kg, measuring 170 cm and 35 years old, is in theory appropriate in weight for gestational age according to the standard definition (SGA), but is in fact suffering from fetal growth restriction in weight. The same child is also theoretically appropriate in length for gestational age, but is in fact suffering from fetal growth restriction in length. These curves can be freely accessed and downloaded on the AUDIPOG website in 3 languages (English, French and Spanish)

Biological criteria

The biological criteria, studied in the Lyon sub-cohort, were the cord blood growth factors IGF1 and IGFBP3. From a 3 ml sample of cord blood, collected at birth, IGF1 was measured by RIA according to Sassolas [21], and IGFBP3 by Immunotech-IRMA using mouse monoclonal antibodies [IRMA–IM1992 by Beckman]. In this sub-cohort, according to the above models, we identified 608 infants as FGR_W (type I or II) and/or FGR_L (type I or II), or as Cs_W and/or Cs_L. These 608 infants were considered as "cases". Cord blood samples had been taken in 453 of these cases. One control was associated with each of these cases, with cord blood samples taken and diagnosed as normal, i.e. no FGR_W, no FGR_L, no SGA_W and no SGA_L. Controls were selected so as to respect the same distribution of gestational age and sex among cases and controls. IGF1 and IGFBP3 were then measured in these 453 cases and 453 controls.

Combined classification of newborns according to both FGR_W and/or FGR_L–clinical and biological characteristics

Considering birth weight and birth length simultaneously, an infant could be classified as no FGR_W–no FGR_L, FGR_W–no FGR_L, no FGR_W–FGR_L or FGR_W–FGR_L. The clinical and biological characteristics were then described for the total cohort and for the Lyon sub-cohort.

Statistical analysis

Clinical results were presented with percentages, biological results were presented with mean values. Statistical analysis used were X^2 test for the comparisons between the percentages and Student *t*-test for the comparisons between the mean values.

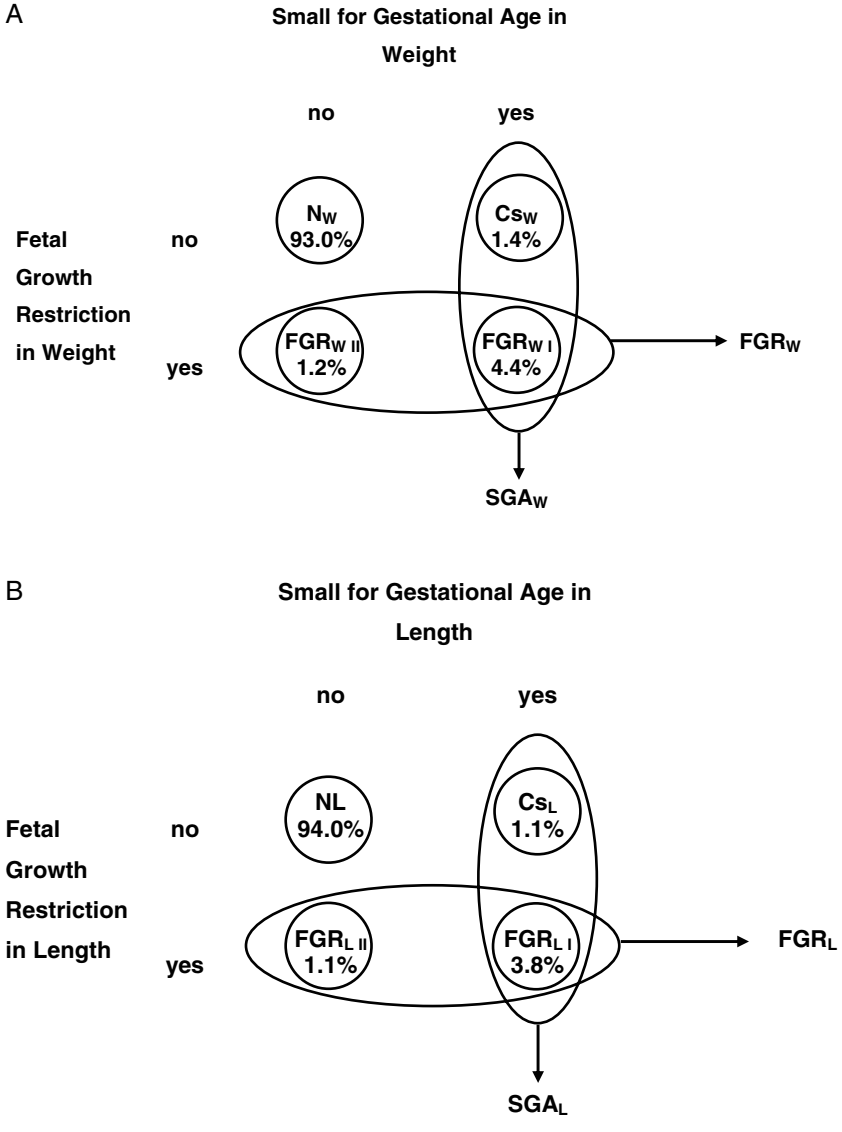

Fig. 2 Identification of four subgroups of newborns according to birth weight whatever birth length (**a**), and according to birth length whatever birth weight (**b**) after taking into account their constitutional growth potential—French AUDIPOG Perinatal Network, *n*=47,733 births 1999–2001. SGA_W: small for gestational age in weight. FGR_W: fetal growth restriction in weight. No SGA_W–no FGR_W = N_W : normal weight. SGA_W–no FGR_W=Cs_W : constitutionally small (thin). No SGA_W–FGR_W= FGR_{WII}: fetal growth restriction in weight –Type II. SGA_W–FGR_W = FGR_{WI}: fetal growth restriction in weight –Type I. SGA_L: small for gestational age in length. FGR_L: fetal growth restriction in length. No SGA_L–no FGR_L = N_L:normal length. SGA_L–no FGR_L= Cs_L: constitutionally small in length. No SGA_L–FGR_L = FGR_{LII} : fetal growth restriction in length –Type II. SGA_L–FGR_L = FGR_{LI} : fetal growth restriction in length –Type I

Results

In the total cohort, 44.5% of the pregnant women were primipareous. The mean maternal age, weight and height were 29.5 ± 5.2 years, 60.9 ± 12.3 kg, and 163.7 ± 6.3 cm respectively. 80.6% of the mothers came from metropolitan France, 6.0% from North Africa, 1.8% from Asia and 4.1% were black people. The mean birth weight and birth length were 3,230.4 ± 581.5 gm and 49.4 ± 2.4 cm respectively. The gestational age varied from 23 to 44 weeks of gestation and 8% of the deliveries occurred before the 37th week.

Statistical models defining FGR_W and FGR_L

Figure 1 presents the FGR_W and FGR_L models accessed on the website: http://audipog.inserm.fr. The first regression model gave the expected LnBW for a particular infant according to its constitutional characteristics and its 5% individualized limit of birth weight ((BW)5%IL). According to its constitutional growth potential, an infant was then classified as "growth-restricted in weight" (FGR_W) if birth weight<(BW)5%IL. The model accounted for 53% of the total variance of birth weight. Similarly, the second regression model for birth length gave the 5% individualized limit of birth length ((BL)5%IL) and allowed us to classify an infant, according to its constitutional growth potential, as "growth-restricted in length" (FGR_L) if birth length<(BL)5%IL. The model accounted for 41% of the total variance of birth length. Ethnic origin brought no additional contribution to either model, once maternal height and pre-pregnancy weight had been taken into account. Moreover, the website gives the predictive fetal growth curves in weight and length. It is not necessary to enter gestational age, birth weight and birth length, but only the characteristics of the mother. The expected birth weight or birth length for a given gestational age is obtained on-screen by positioning the cursor at the appropriate point on the curves.

Classification of newborns as FGR_W or FGR_L according to their constitutional growth potential – clinical and biological results

Figure 2 presents the distribution of infants into the four subgroups identified by crossing classical and new definitions for birth weight (N_W, Cs_W, $FGR_{W\ I}$, $FGR_{W\ II}$). 2.6% of infants appeared to be wrongly classified with the classical approach. Among infants initially classified SGA_W, 24% have to be considered as "constitutionally small" in weight. Similarly, as regards birth length, 2.2% of infants appeared to be wrongly classified with the classical approach. Among infants initially classified SGA_L (5%), 22% have to be considered as "constitutionally small" in length.

Table 1 shows the rates of gravidic hypertension, of Apgar score at 5 min ≤ 6 and the mean values of IGF1 and IGFBP3 respectively, in the groups defined by FGR_W, by SGA_W, and in the four subgroups obtained by crossing FGR_W and SGA_W.

The rates of gravidic hypertension and of Apgar score at 5 min ≤ 6 are significantly lower in the "no FGR_W" group (3.7% and 1.1% respectively) than in the FGR_W group (13.6% and 2.9% respectively). Moreover, the rates of gravidic hypertension and of Apgar score at 5 min ≤ 6 differ significantly between each for the $FGR_{W\ II}$ and $FGR_{W\ I}$ subgroups and the N_W subgroup. The $FGR_{W\ II}$ subgroup has higher rates of gravidic hypertension and of Apgar score at 5 min ≤ 6 (19.9% and 3.9% respectively).

Table 1 Clinical and biological characteristics of the infants according to the new definition of "fetal growth restriction in weight" after taking constitutional growth potential into account and according to SGA in weight definition—French AUDIPOG perinatal network 1999–2001 (47,733 infants) and Lyon sub-cohort (906 infants with blood samples)

		No.	Gravidic hypertension (%)		Apgar≤6 at 5 min (%)		No.	IGF1(ng/ml) Mean ± SEM		IGFBP3 (μg/ml) Mean ± SEM	
New classification											
No FGR_w	N_W	44,380		3.7		1.1	565		151.9±1.5		1.13±0.01
	Cs_W	662		2.2§		0.8NS	74		131.9±3.8*		1.04±0.04†
	Combined		3.7		1.1			149.6±1.4		1.12±0.01	
FGR_w	$FGR_{W\ II}$	564		19.9*		3.9*	58		131.0±3.9*		0.92±0.04*
	$FGR_{W\ I}$	2127		12.0*		2.7*	209		131.5±2.3*		0.91±0.02*
	Combined		13.6*		2.9*			131.4±2.0*		0.91±0.02*	
Standard classification											
No SGA_W		44,944	3.9		1.1		623	150.0±1.4		1.11±0.01	
SGA_W		2789	9.6*		2.2*		283	131.6±2.0*		0.94±0.02*	

N_W: Normal Weight. Cs_W: Constitutionally small in Weight. $FGR_{W\ II}$: Fetal Growth Restriction in Weight – Type II. $FGR_{W\ I}$: Fetal Growth Restriction in Weight – Type I

p value between no FGR_W and FGR_W, between no SGA_W and SGA_W, and between N_W and the other groups: § <0.05; † <0.01; ‡ <0.001; *<10^{-4}

The mean values of IGF1 and IGFBP3 are significantly lower in the FGR_W group (131.4 ± 2.0 and 0.91 ± .02 respectively) than in the "no FGR_W" group (149.6 ± 1.4 and 1.12 ± 0.01 respectively). The mean values of IGF1 and IGFBP3 differ significantly between each for the $FGR_{W\ II}$ and $FGR_{W\ I}$ subgroups and the N_W subgroup. It can be seen that in the Cs_W subgroup the mean value of IGFBP3 is close to that of N_W, whereas the mean value of IGF1 is close to that of $FGR_{W\ I}$ or $FGR_{W\ II}$.

When comparing the FGR_W new definition to the SGA_W standard definition, the rates of gravidic hypertension and of Apgar score at 5 min ≤ 6 seem to be higher in the FGR_W group (13.6% and 2.9% respectively) than in the SGA_W group (9.6% and 2.2% respectively).

Table 2 shows the rates of gravidic hypertension, of Apgar score at 5 min ≤ 6 and the mean values of IGF1 and IGFBP3 respectively in the groups defined by FGR_L, by SGA_L, and in the four subgroups obtained by crossing FGR_L and SGA_L.

In the same way, the rates of gravidic hypertension and of Apgar score at 5 min ≤ 6 are significantly lower in the "no FGR_L" group (3.6%, 0.6% respectively) than in the FGR_L group (8.9%, 1.1% respectively). Moreover, the rates of gravidic hypertension differ significantly between each for the $FGR_{L\ II}$ and $FGR_{L\ I}$ subgroups and the N_L subgroup, and the rates of Apgar score at 5 min ≤ 6 differ significantly between the $FGR_{L\ I}$ subgroups and the N_L subgroup. The $FGR_{L\ II}$ subgroup has higher rates of gravidic hypertension and of Apgar score at 5 min ≤ 6 (12.4% and 1.2% respectively).

The mean values of IGF1 and IGFBP3 are significantly lower in the FGR_L group (131.7 ± 2.3 and 0.96 ± 0.02 respectively) than in the "no FGR_L" group (147.7 ± 1.4 and 1.09 ± 0.01 respectively). The mean values of IGF1 and IGFBP3 differ significantly between each for the $FGR_{L\ II}$ and $FGR_{L\ I}$ subgroups and the N_L subgroup.

Combined classification of newborns according to both FGR_W and/or FGR_L – clinical and biological results

By combining FGR_W and FGR_L (Fig. 3), we obtained four groups called: (1) not growth-restricted in weight or in length (no FGR_W–no FGR_L: 92.4% of infants), (2) growth-restricted in weight but not in length (FGR_W–no FGR_L: 2.7% of infants), (3) growth-restricted in length but not in weight (no FGR_W–FGR_L: 2.6% of infants), and (4) growth-restricted in weight and in length (FGR_W–FGR_L: 2.3% of infants).

Table 3 shows the results for the four groups as defined above in terms of maternal hypertension, Apgar score, and IGF1 and IGFBP3 levels. It appears that higher rates of maternal hypertension are observed in the groups diagnosed FGR_W–FGR_L (13.1%) and FGR_W–no FGR_L (9.6%), showing that higher gravidic hypertension negatively affects weight growth. The lowest Apgar coefficients (1.5% and 1.1%, respectively) were found in these groups. The lowest mean values of IGF1 and IGFBP3 were obtained in the group of infants growth-restricted both in weight and in length (FGR_W–FGR_L).

Table 4 shows the rates of gravidic hypertension, of Apgar score and the mean values of IGF1 and of IGFBP3 for three subgroups that were isolated from the no FGR_W–no FGR_L infants because of the low IGF1 mean value in the Cs_W subgroup. Those three subgroups are the "totally normal" subgroup (N_W–N_L: 90.5%), the "familial shortness" subgroup (N_W–Cs_L: 0.9%) and the "familial thinness" subgroup (Cs_W whatever length: 1.0%). All these infants were clinically normal (maternal gravidic hypertension of 3.4%, 1.5%, 2.1% respectively and Apgar score of 0.6%, 0.0%, 1.0% respectively), but the Cs_W-only subgroup had lower mean values of IGF1 and IGFBP3 than in the totally normal subgroup.

Table 2 Clinical and biological characteristics of the infants according to the new definition of Fetal Growth Restriction in length after taking constitutional growth potential into account and according to SGA in length definition – French AUDIPOG perinatal network 1999–2001 (47,733 infants) and Lyon sub-cohort (906 infants with blood samples)

		No.	Gravidic hypertension (%)	Apgar≤6 at 5 min (%)	No.	IGF1(ng/ml) Mean ± SEM	IGFBP3 (μg/ml) Mean ± SEM
New classification							
No FGR_L	N_L	41,078	3.6	0.6	665	147.9±1.4	1.09±0.01
	Cs_L	461	1.7§	0.2^{NS}	39	$144.3±4.5^{NS}$	$1.12±0.04^{NS}$
	Combined		3.6	0.6		147.7±1.4	1.09±0.01
FGR_L	FGR_L I	493	12.4*	1.2^{NS}	52	134.0±4.3†	$1.00±0.03^{§}$
	FGR_L II	1652	7.8*	1.1§	138	130.8±2.7*	0.94±0.02*
	Combined		8.9*	1.1†		131.7±2.3*	0.96±0.02*
Standard classification							
No SGA_L		41,571	3.7	0.6	717	146.9±1.4	1.08±0.01
SGA_L		2113	6.5*	0.9^{NS}	177	133.8±2.4*	0.98±0.02*

N_L: Normal Length. Cs_L: Constitutionally small in Length. $FGR_{L\ II}$: Fetal Growth Restriction in Length – Type II. $FGR_{L\ I}$: Fetal Growth Restriction in Length – Type I

p value between no FGR_L and FGR_L, between no SGA_L and SGA_L and between N_L and the other groups: §<0.05; †<0.01; ‡<0.001; *$<10^{-4}$

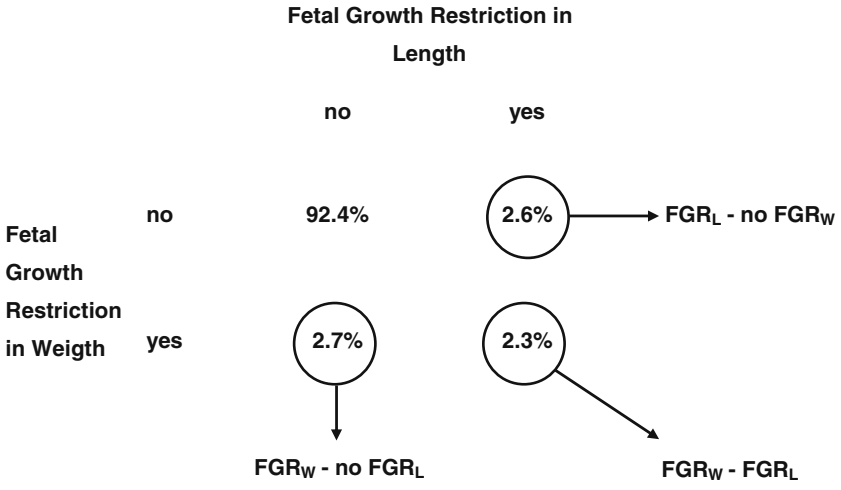

Fig. 3 Identification of four subgroups of newborns according to birth weight and birth length, after taking into account their constitutional growth potential – French AUDIPOG Perinatal Network *n*=47,733 births 1999–2001. No FGR_W–no FGR_L= no fetal growth restriction in weight and length. FGR_W–no FGR_L= fetal growth restriction in weight but not in length. FGR_L–no FGR_W = fetal growth restriction in length but not in weight. FGR_W–FGR_L = fetal growth restriction in weight and length

Comment

This study was aimed at identifying newborns with fetal growth restriction in weight and/or length. Considering the individual growth potential of infants, we were able to identify two new subgroups of infants, $FGR_{W\ II}$ or $FGR_{L\ II}$, usually combined with normal infants and who showed high rates of maternal hypertension and poor neonatal adaptation. The $FGR_{W\ II}$ and/or $FGR_{L\ II}$ infants, usually not recognized as SGA, represent 1.7% of the total cohort. Considering birth length, and not only birth weight, as recommended by Lee et al. [15], we were able to identify a group of infants who were FGR in length, but not in weight, usually not recognized as SGA at birth. This group represents 2.7% of the total cohort. Infants with FGR_W–FGR_L had the poorest neonatal adaptation and the lowest IGF1 and IGFBP3 levels.

Our approach can be challenged on some methodological points. As previously stated by other authors, mothers with gravidic pathology have not to be excluded, these circumstances being considered as risk factors for FGR-like tobacco consumption [7]. According to the proceedings of the recent consensus conference, we also did not exclude multiple pregnancies [15]. Considering the normal threshold values for SGA as well as for FGR, we chose the 5th centile rather than the 10th, as suggested by Goldenberg [7], and were able to verify that in our population infants<5th centile had a worse neonatal status than those between the 5th and 10th centile (2.2% of SGA in weight infants defined by the 5th centile had an Apgar score at 5 min ≤ 6 as against 1.8% of those defined between the 5th and the 10th centile). Considering the maternal characteristics to be entered into the models, maternal age, parity, pre-pregnancy weight and height were considered by other authors as "physiological birth-weight determinants" [3, 20, 21]. Like us, they considered tobacco, hypertension and alcohol/toxic consumption as factors leading to impaired fetal growth, which for that reason should not be entered into the model. We found that ethnic origin did not further improve the models after taking the other maternal characteristics into account. This result is in keeping with Goldenberg's point of view, i.e. "low birth weights in black people can be explain by an excess of risk factors in this racial group rather than by a different

Table 3 Clinical and biological characteristics of infants into four groups related to both weight and length, after taking constitutional growth potential into account – French AUDIPOG perinatal network 1999–2001 (47,733 infants) and Lyon sub-cohort (906 infants with cord blood samples)

Characteristics Group of newborns	No.	Gravidic hypertension (%)	Apgar≤6 at 5 min (%)	No.	IGF1 (ng/ml) Mean ± SEM	IGFBP3 (μg/ml) Mean ± SEM
No fetal growth) restriction: no FGR_W–no FGR_L	40,343	3.4	0.6	539	152.1±1.5	1.13±0.01
Fetal growth restriction in length but not in weight: FGR_L–no FGR_W	1121	5.0†	0.8^{NS}	99	136.7±3.2*	1.05±0.03†
Fetal growth restriction in weight but not in length: FGR_W–no FGR_L	1196	9.6*	1.1§	165	133.3±2.5*	0.94±0.02*
Fetal growth restriction in weight and in length: FGR_W and FGR_L	1024	13.1*	1.5‡	91	126.2±3.2*	0.86±0.03*

FGR_W : Fetal Growth Restriction in Weight. FGR_L : Fetal Growth Restriction in Length
p value between no FGR_W–no FGR_L and the other groups: § <0.05; † <0.01; ‡ <0.001; *<10^{-4}

Table 4 Clinical and biological characteristics into three subgroups among the no FGRW–no FGRL infants: French AUDIPOG perinatal network 1999–2001 (47,733 infants) and Lyon sub-cohort (906 infants with cord blood samples)

Characteristics Subgroup of the no FGR_W–no FGR_L newborns	No.	Gravidic hypertension (%)	Apgar at 5 min≤6 (%)	No.	IGF1 (ng/ml) Mean ± SEM	IGFBP3 (μg/ml) Mean ± SEM
Normal: N_W–N_L	39,550	3.4	0.6	453	154.9±1.7	1.14±0.014
Familial shortness: Cs_L	378	1.5^{NS}	0.0^{NS}	32	$145.0±4.9^{NS}$	$1.17±0.039^{NS}$
Familial thinness: Cs_W-only	415	2.1^{NS}	1.0^{NS}	54	132.3±4.9*	$1.02±0.047^{\dagger}$

N_W: Normal Weight. Cs_W-only: Constitutionally small in Weight only. N_L: Normal Length. Cs_L: Constitutionally small in Length
p value between N_W–N_L and the other groups: § <0.05; † <0.01; ‡ <0.001; *$<10^{-4}$

constitutional growth potential" [7]. Paternal height, which might also be considered as a constitutional determinant of birth weight and birth length, was not available in our database. However, Lazar et al. indicated that, because of the strong statistical correlation between paternal and maternal height, paternal height did not further contribute to birth weight [14]. We used a backwards stepwise multiple regression analysis for calculating a predicted birth weight according to "physiological birth weight determinants" in the same way as Sanderson [20]. Recently, Clausson also introduced the notion of an "individualized growth curve" [5].

Groups newly identified as $FGR_{W\ II}$ and $FGR_{L\ II}$ are associated with higher incidences of gravidic hypertension, and with lower Apgar scores, than classically-identified $FGR_{W\ I}$ and $FGR_{L\ I}$. The association between gravidic hypertension and impaired fetal growth is well-known [24]. The highest rates of maternal hypertension in the new $FGR_{W\ II}$ and $FGR_{L\ II}$ subgroups may be related to a more homogeneous aetiology of growth restriction in these infants than in the classically-identified groups. The cord blood levels of IGF1 and IGFBP3 were similar in $FGR_{W\ I}$ and $FGR_{W\ II}$, and also in $FGR_{L\ I}$ and $FGR_{L\ II}$. These results brought a complementary validation of our models. The IGF1 and IGFBP3 rates were lower in all groups of growth-restricted infants than in the non-restricted group, which accords with results already published [16, 22]. Klauwer showed that IGF1 and IGFBP3 were better correlated with birth weight than with birth length [12].

Our results show that the FGR new definition permits the identification of a subgroup even more pathologic than $FGR_{W\ I}$, as the $FGR_{W\ II}$ subgroup has rates of gravidic hypertension and of Apgar score at 5 min ≤ 6 higher than in the $FGR_{W\ I}$ subgroup. The Cs_W subgroup has rates of gravidic hypertension and of Apgar score at 5 min ≤ 6 very close to and even smaller than those of the N_W subgroup.

Among the non-restricted infants, and because of the low IGF1 mean value of Cs_W we propose to isolate "familial thinness" infants who showed lower rates of IGF1 and IGFBP3 than in "normal" infants. This result could be in keeping with the hypothesis of an inadequate fetal nutrition in relation to the thinness of the mothers [16]. In fact, these "thinness" infants were born from slightly-short mothers (mean height 161 cm vs 163 cm in the "normal" group) with a low Body Mass Index (mean BMI 19.8 vs 22.0 in the "normal» group, results not shown). Nonetheless this situation of underfed women, at least in developed countries, does not seem to alter neonatal adaptation. Even though these infants had a good neonatal adaptation, they could show worse post-natal growth, possibly requiring growth hormone treatment, given their low levels at birth. It is interesting to notice that the growth-restricted infants had mothers of normal height like non-restricted infants (mean value 163 cm). Conversely, the "familial shortness" infants were born from short mothers (mean height 156 cm vs 163 cm in the "normal" group) and showed IGF1 and IGFBP3 rates which did not differ from those of "normal" infants.

From an epidemiological point of view, the recurrent debate about universal and/or local growth curves can be solved thanks to the notion of constitutional growth potential and FGR. Since the ethnic origin does not make any contribution to the models after taking maternal characteristics into account, we believe that our models could be used everywhere to shed light on variations of FGR incidence from one country to another, and to detect environmental conditions which influence fetal growth, regardless of constitutional factors.

From a clinical point of view, an individualized definition of FGR based on constitutional growth potential, considering birth length and not only birth weight, will allow the identification of at-risk infants that have not been recognized as such, without confusing them with normal infants. Namely, the definition of FGR will allow the identification in France (800,000 deliveries per year) of 26,000 infants with FGR in weight and/or in length not yet recognized as small with the standard SGA definition based only on weight and without taking growth potential into account. Using this new definition should help to change the usual criteria of neonatal transfer at birth, to better recognize infants requiring post-natal growth follow-up, to revisit the indication criteria of growth hormone treatment, and to understand the fetal origin of adult diseases.

We are well aware that only the long-term outcome will ultimately validate our model. For this reason we are currently tracking a cohort of more than 600 infants classified according to our model.

Acknowledgements This work is dedicated to the memory of Dr J. M. Saez. We are indebted to Dr J.Y. Lebouc (INSERM unit 515, Paris) and to Pr P. Chatelain (Hospices civils de Lyon) for their advice.

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