CHAPTER 10

Maternal factors, fetal development and pregnancy outcome

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Abstract

Low birth weight is the main determinant of infant mortality, affects the healthy development of the newborn, and determines the differential risk of developing chronic diseases in advanced stages of the life cycle. In Spain, as in other Western countries, low birth weight and prematurity have increased significantly in recent years. Therefore, to know the **fetal** growth **trajectories** and to identify the factors responsible for such differences is of great interest for Perinatal Medicine and Human Ecology. This paper aims to identify the maternal factors that are generating variability in fetal growth, as well as to evaluate their influence on different segments and at different stages of fetal development. A sample of 1404 mothers/newborns pairs studied between 2006 and 2008 at the Maternity Hospital "La Paz", Madrid (Spain) is analyzed. The results show that the inclusion of these variables of the Maternal System allows a deeper evaluation of optimal fetal development: these maternal variables reflect both the different biological, emotional and social aspects of the environment in which the mother grew up, and the conditions in which the foetus spends the first stage of prenatal life, allowing the evaluation of

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the favorableness of the intrauterine development, essentially at birth and by means of the weight and the height of the newborn.

Key words: *Optimal fetal development*, *Maternal System*, *Plasticity*.

Introduction

Low birth weight (with or without prematurity) is the main determinant of infant mortality, affects the healthy development of the newborn, and determines the differential risk of developing chronic diseases in advanced stages of the life cycle (Barker, 1997; Drake and Walker, 2004; Ellison, 2005; Kuzawa and Pike, 2005; Varela-Silva et al., 2009, Bogin and Varela-Silva, 2010). Paradoxically, since the eighties a tightly controlled infant mortality rate has evolved together with a slow but steady rise in premature and low weight births, both in Spain (Figure 10.1) as in other Western countries (Varea et al., 2012). This fact, which worries professionals and those responsible for health policy, suggests that something is not working in perinatal health prevention. The WHO (2006) recommends that once deaths are tightly controlled, perinatal intervention should be directed towards the functional improvement of newborns to enable optimum fetal development, that which gives newborns the highest probability of surviving and growing during their postnatal transition and their first year, so that the effects of the early stages of development do not have a negative influence on their life cycle.

Generally, evaluation of fetal development is based on pregnancy outcome, measured in gestation age, birth weight and the relation between these variables. However, birth weight as an indicator of perinatal health is only useful up to a point: firstly, because it simultaneously reflects all aspects of fetal growth and development, and does not distinguish between a short pregnancy and insufficient fetal growth (WHO, 2006); secondly, because birth height is not the only route associated with permanent phenotypic changes which lead to adult illnesses. Most publications analyze the physiological responses to stress situations caused by malnutrition, which take place in the early stages of development. Individuals exposed to undernourishment in the early stages of development respond by means of integrated physiological mechanisms which increase energy efficiency and reduce fat oxidization, giving rise to phenotypes which combine short legs and small stature with increased adiposity (Frisancho, 2007). It has been shown that other factors of the maternal environment, such as smoking (Lampl et al., 2003) or psychosocial stress (Pike, 2006), can also alter fetal development and provoke anatomical and physiological changes with long-term effects on health. Thus, the analysis of other anthropometric indicators of newborns (height and cephalic perimeter) and of fetal anthropometry in the second and third terms can provide more accurate information about the stress situations which affect fetal development, about possible differential responses of corporal segments and about the biological mechanisms which allow adjustment to these situations.

Optimum fetal development requires mothers to be in good mental and physical health before and during pregnancy. For this reason, the WHO (2006) considers that, apart from fetal and newborn anthropometry, the evaluation of optimum fetal development should include factors of the so-called "*Maternal System*", which define intrauterine environment characteristics, among others, age, nutritional and emotional state, tobacco and alcohol consumption, height and menarchy age, which help to evaluate the favourableness of maternal development. For this very reason, identifying the Maternal System factors which help to explain differences in fetal development at different gestational ages and in different corporal segments is of great interest to human ecology and perinatal medicine. By using fetal and newborn indicators simultaneously, this study has two aims: a) to identify which maternal factors (biological, psychosocial and socio-cultural) best explain variations in fetal growth; and b) to evaluate whether the same maternal factors affect the same corporal segments at different stages of fetal development (second term, third term and at birth).

Material and methods

A transversal sample of 1,404 pairs of mothers/newborns was analyzed, based on the clinical histories and complementary surveys carried out between 2006 and 2008 in the Maternity Hospital "La Paz", Madrid, Spain. Furthermore, there is anthropometric information about fetal development for 472 of these pairs, which was obtained through ecography in the second and third terms of pregnancy. The anthropometrical fetal indicators the second and third terms are the biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC), and for the newborns, length gestation, cephalic perimeter (CP), weight and height, and also body mass index (BMI).

The variables in the Maternal System include the mother's biological, cultural and psychosocial indicators, both before and during pregnancy. A general linear model (GLM) for each of the indicators for fetal and newborn growth was prepared, introducing all the maternal variables for each one so as to identify whether sensitivity to maternal factors is similar in the different indicators of fetal growth, and whether it differs depending on the stage of development (second term, third term and at birth).

To group them by term and to increase available data, the values for fetal variables have been normalised for each week of gestation, grouping those which correspond to weeks 19-22 (second term) and those which correspond to weeks 28-32 (third term). The statistical programme used was SPSS 15.

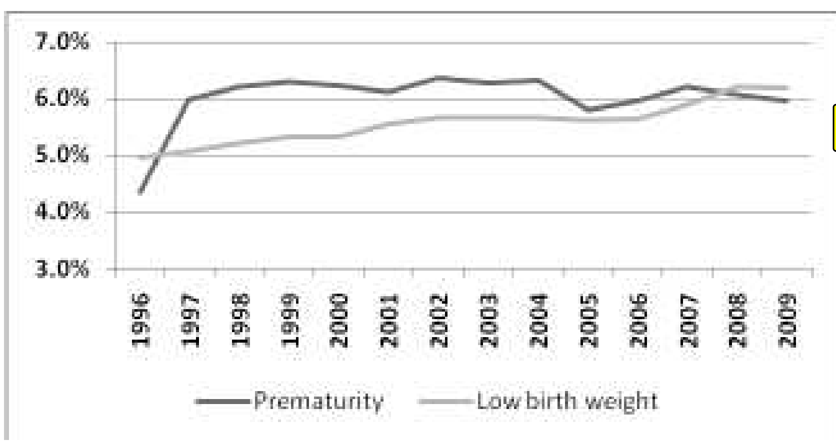

Figure 10.1 Temporal increase in low birth weight (< 2500 g) and preterm births (<37 weeks)
(Spain, 1996-2009, single births and Spanish mothers)

Results

Table 10.1 shows biological indicators for the Maternal System related to conditions of development (height and age of sexual maturity), before pregnancy (weight and BMI) and during pregnancy (total weight gained and weight gained each term, and haemoglobin levels at the end of pregnancy). Table 10.2 shows the combined psychosocial and behavioural maternal factors analyzed in this study. Whereas Table 10.3 shows fetal anthropometry (BPD, FL and AC) in gestation weeks 19-32, Table 10.4 shows the corresponding values for anthropometric variables at birth (weight, height, CP and BMI) according to gender.

Ten GLMs (General Lineal Model) were carried out to evaluate the effects of maternal variables on fetal development, one GLM for each of the fetal development variables in the two trimester analized (6 in total) and for each of the newborn traits (4 in total). Results are summarized in Table 10.5. All maternal variables shown in Table 10.1 and 10.2 were introduced in each analysis, though results shown in Table 10.5 only include those which were predictable for at least one model. Finally, Table 6 shows the same results only for the 4 variables for newborns but incorporating the maturity variable, which, while not significantly affecting fetal indicators, does affect newborn variables (the results are basically the same as those in Table 10.5 but the variability explained in the model greatly increases).

AC is the least variable of fetal development indicators in terms of maternal factors, and does not show any significant model for either term. BPD is the most influenced by maternal factors, showing significant models in both terms. Finally, no significant influences on FL were detected in term two, although there were in term three. As for anthropometric variables at birth, weight and height are the fetal indicators most clearly explained by maternal factors, while neither CP nor BMI show significant models.

Table 10. 1 Maternal System: biological markers (before pregnancy and along pregnancy) (Maternity Hospital “La Paz”, Madrid, Spain)

Maternal System: biological markers	*N*	*Mean (sd)*	*P10*	*P25*	*P50*	*P75*	*P90*
Maternal age (years)	1,285	30.31 (5.78)	22	26	31	31	3
Age at menarche (years)	1,171	12.84 (1.15)	11	12	13	14	15
Height (cm)	798	162.95 (6.75)	154	159	163	168	172
BMI (before pregnancy) (kg/m^2)	860	23.67 (446)	19.37	20.81	22.85	25.53	29.37
Haemoglobin (mgr/dl)	1,196	12.43 (1.54)	10.5	11.6	12.6	13.5	14.2
Weight increase (1^{st} trimester) (kg)	277	2.86 (2.24)	0	1.5	3	4	6
Weight increase (2^{nd} trimester) kg)	273	4.32 (2.28)	2	3	4	6	7
Weight increase (3^{d} trimester) (kg)	275	4.99 (2.80)	2	3	4.5	6	8
Total weight increase (kg)	914	12.04 (4.76)	7	9	12	15	18

Table 10.2 Maternal System: cultural and psychosocial markers (Maternity Hospital “La Paz”, Madrid, Spain)

Maternal System: psycosocial and cultural markers	*n (N)*	*Frequency (%)*
Sikness (*yes*) trimestre 1	363 (898)	59.5
Vómiting (*yes*) trimestre 1	450 (896)	50.2
Craving (*yes*)	335 (817)	37.8
Working outside home during pregncy (*yes*)	695 (96)	72.2
Smoking during pregnancy (*yes*)	192 (1,164)	16.5
Civil status (not married)	235 (1,149)	83
Unplanned pregnancy (*yes*)	121 (772)	15.7
Education		
Primariy (not completed)	21 (435)	2.5
Primary	123 (435)	8.8
Higth School	273 (435)	19.4
Technical/College degree (3 years)	179 (435)	12.7
Postgraduate (4-5 years)	370 (435)	26.4
Ethnicity		
Spain	566 (995)	56.9
Maghreb	68 (995)	6.8
Latin America	279 (95)	28
East Europe	82 (995)	8.2

Table 10.3 Anthropometric indicators for fetal development (Maternity Hospital "La Paz", Madrid, Spain)

	Fetal anthropometry					
Gestational age	*BPD (mm)*		*AC (mm)*		*FL (mm)*	
	n	*Mean (sd)*	*n*	*Mean (sd)*	*n*	*Mean (sd)*
19	209	45.54 (2.67)	156	143.09 (9.75)	208	30.10 (2.22)
20	209	47.74 (3.07)	154	150.70 (10.21)	208	32.05 (3.09)
21	48	49.82 (2.88)	33	156.02 (12.34)	46	33.76 (4.08)
22	14	50.21 (4.99)	10	159.34 (17.25)	15	35.99 (9.06)
28	18	72.04 (4.10)	15	243.15 (13.47)	17	52.04 (2.16)
29	11	77.64 (5.90)	6	252.33 (18.55)	12	55.47 (4.65)
30	30	76.31 (5.00)	21	258.66 (21.43)	30	57.14 (4.22)
31	79	79.75 (3.40)	59	269.65 (14.90)	78	59.74 (3.22)
32	139	82.19 (3.17)	97	278.83 (12.62)	140	62.27 (5.07)

(AC: abdominal circumference; BPD: biparietal diameter; FL: femur length.)

Table 10.4 Sexual diferences in new born anthropometry and in gestation lenght (Maternity Hospital "La Paz", Madrid, Spain)

	Gestational Age (weeks) (**)		*Weight (gr) (***)*		*Height (cm) (*)*		*CC (cm) (**)*		*BMI (kg/cm²) (ns)*	
Sex (new born)	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)
Male	626	38.83 (1.75)	634	3,260.83 (480.65)	425	48.86 (2.69)	425	34.68 (2.07)	424	13.76 (2.07)
Female	646	39.09 (1.64)	650	3.168 (449.58)	459	48.47 (2.51)	459	34.28 (1.77)	457	13.73 (2.56)
Total	1,280	38.96 (1.707)	1,287	3.213.82 (466.83)	888	48.66 (2.60)	888	34.47 (1.93)	884	13.74 (2.33)

(CC: Cephalic circumference; BMI: Body Mass Index; ns, not significant; *(*p*<, 05); **(*p*<, 01); ***(*p*<001.)

Table 10.5 Results of 10 different GLMs analysis explaining the contribution of maternal biological and psychosocial markers on each trait used to evaluate fetal development. (Maternity Hospital "La Paz", Madrid, Spain).

Variables in (second trimester)	*Fetal anthropometry (third trimester)*			*Fetal anthropometry anthropometry*			*New born the Models*			
	BPD (n=202)	*AC (n=151)*	*FL (n=200)*	*BPD (n=111)*	*AC (n=72)*	*FL (n=111)*	*Weight (n=512)*	*Height (n=387)*	*CC (n=386)*	*BMI (n=385)*
F (*p*)	2.092 (*)	ns	ns	1.88 (*)	ns	1.878 (*)	10.008 (***)	2.035 (*)	ns	ns
R^2(%)	12.1			17.8		17.7	14.5	6.5		
Sex	*									
Maternal age	*									
Heigth							*			
Age at menarche						*	*	*		
BMI before pregnacy	*			*		*	**	*		
Total weight increase	*						***	*		
Craving	*					*	*	*		
Ethnicity				*		*		*		
Education								**		
Smoke	*					*	**			

(BPD: biparietal diameter; AC: abdominal circumference; FL femur length, CC: Cephalic circumference; BMI: Body Mass Index; ns, not significant; *(p<05); **(p<01); ***(p<001.)

As for as maternal factors which explain the variability of fetal development indicators, maternal BMI before pregnacy (nutritional indicator which contributes to the five significant models) and cravings (psychosocial indicator which contributes to four) are the variables which best explain variability in fetal development as a whole. The age of sexual maturity – which gives information about the early conditions of maternal development- helps to explain femoral growth during the third term, and variability in height and weight at birth. Among social variables, maternal origin explains variability in fetal development in the third term (both BPD and FL), as well as in height at birth. Smoking during pregnancy affects fetal development in the second term (BPD) and third term (LF), as well as newborn weight. Finally, the level of education only influences height at birth.

Discussion

Incorporating the Maternal System variables allows a better interpretation of the variability found in fetal development. Maternal factors reflect the different biological, social, emotional and behavioural aspects which make up the unique environment in which the mother developed and in which the foetus finds itself in the prenatal stage of life. Four aspects of the results may be evaluated. The first refers to a demonstration that even in populations with a high standard of living nutritional aspects (pre-pregnancy BMI and total weight gained during pregnancy) contribute significantly to the variability which exists in fetal development, both when this is analysed in the second and third terms of gestation, as when it is done at birth. This may have implications for the prevalence of obesity and cardio-vascular risks in advanced stages in life (Barker, 2001). The second aspect is establishing that the very same environmental circumstances which typified the mother's development (measured through age of sexual maturity and height) have a significant influence on both fetal development (FL) and weight and height at birth. Thirdly it was seen that of the three psychosocial variables (cravings, vomiting and sikness) included in the study, only cravings significantly influence both fetal and newborn development. In the sample analyzed, 58.3% of the women had nausea, 48.8% vomited and 32.7% had cravings (Bernis, 2009). Nozal and Mateos (2010) offer an adaptive interpretation to explain such a high incidence in the population. Finally, the influence of smoking on fetal development (BPD and FL) and on birth weight was confirmed. Lampl et al. (2003) also found negative effects of smoking on fetal femoral development, and Leary et al. (2006) observed that smokers' children consistently have significantly shorter limbs during post-natal development than the children of non-smokers.

Table 10.6 Results of GLMs, adding Maturity (gestational age) to the set of variables introduced in previous analysis shown in Table 10.5. Only results relative to new born are shown as maturity does not significantly affect fetal development in 2nd and 3d trimesters. (Maternity Hospital "La Paz", Madrid, Spain).

	New born anthropometry			
Variables in the Model	*Weigh(n=512)*	*Height(n=387)*	*CC(n=386)*	*BMI(n=385)*
F (*p*)	10.008 (***)	2.216 (**)	ns	ns
R^2 (%)	36.9	8.0		
Sex	*			
Maturity	***			
Maternal age				
Maternal Heigh	*			
Age at menarche	*	*		
BMI before pregnancy	**			
Total weight gain	***	*		
Craving	*	*		
Ethnicity		*		
Education				
Smoking	*******			

(CC: Cephalic circumference; BMI: Body Mass Index; ns, not significant; *, *p*<, 05; **, *p*<, 01; ***, *p*<, 001.)

The first studies to associate fetal programming with permanent phenotypic changes in adults showed that unfavourable intrauterine environments (evaluated by birth weight) were connected with more abdominal fat and less lean body mass in adults (Barker, 1997, 2002; Hales and Barker 2001; Lampl and Jeanty 2004). More recently (Frisancho, 2007) it has been shown that people with short limbs in proportion to their height are significantly more adipose than those with longer limbs. The relative contribution of legs to total height has long been considered an excellent biomarker for early environmental conditions (Frisancho et al., 2001). Demonstrating the link with adiposity, combining adult phenotypes with short limbs and high adiposity is also interpreted as the result of physiological adjustments carried out by foetuses subjected to stress situations during the sensitive stages of development. Initially, these plastic responses were associated with nutritional stress (Ravelli et al., 1999), although later results

(Frisancho, 2007; Lampl et al., 2003) suggest that they may also stem from the effect of other stressful factors, either emotional or psychosocial, or from smoking, among others.

The results obtained also suggest contrasts to the hypothesis of intergenerational heredity as proposed by Varela-Silva et al. (2009), firstly because weight and, specially, length of legs are indicators which are being studied to prove this effect (Floyd, 2008; Varela-Silva et al., 2009; Jasienska 2009), and secondly because the mothers' age at sexual maturity explains an important part of variability in femur length in the third term, and height and weight at birth. Schooling et al. (2010) suggest that gender differences exist in the length of legs measured by estrogen levels, and it is known that ovary estrogen levels during fertile life are linked to the conditions of development of women and possibly those of their mothers too.

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