Intrauterine Growth Retardation, edited by Jacques Senterre. Nestlé Nutrition Workshop Series, Vol. 18. Nestec Ltd., Vevey/Raven Press, Ltd., New York © 1989.

Risk Factors Associated with Intrauterine Growth Retardation in Developed Countries: Italy as an Example

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PATHOPHYSIOLOGY

Intrauterine growth retardation (IUGR) can result from a variety of environmental or genetic influences of fetal growth (1). However, the pathophysiology is still not completely understood, although the lack of transport of sufficient quantities of nutrients and oxygen to the fetus is commonly recognized as the endpoint causing IUGR (2). Genetic, metabolic, and nutritional factors cannot be viewed totally independently, but in some ways are interrelated (Fig. 1) (3).

From the studies of Naeye and Tafari (4), based on data collected in the U.S.A. (Collaborative Perinatal Project), several aspects appear to point towards a deficiency of utero-placental blood flow, due either to a lack of expansion of plasma volume during pregnancy or to an impairment of microcirculation at the placental level. This fact complicates pre-existing negative factors, like undernutrition or living at high altitude, and is further aggravated by exposure to a toxic environment.

Two examples substantiate the concept that the increase in plasma volume during pregnancy is very important in allowing good intrauterine growth. The first example

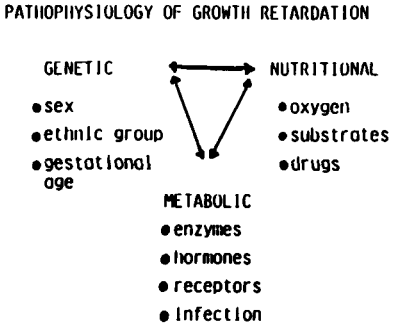

FIG. 1. The major factors that determine fetal growth and development. (From ref. 3.)

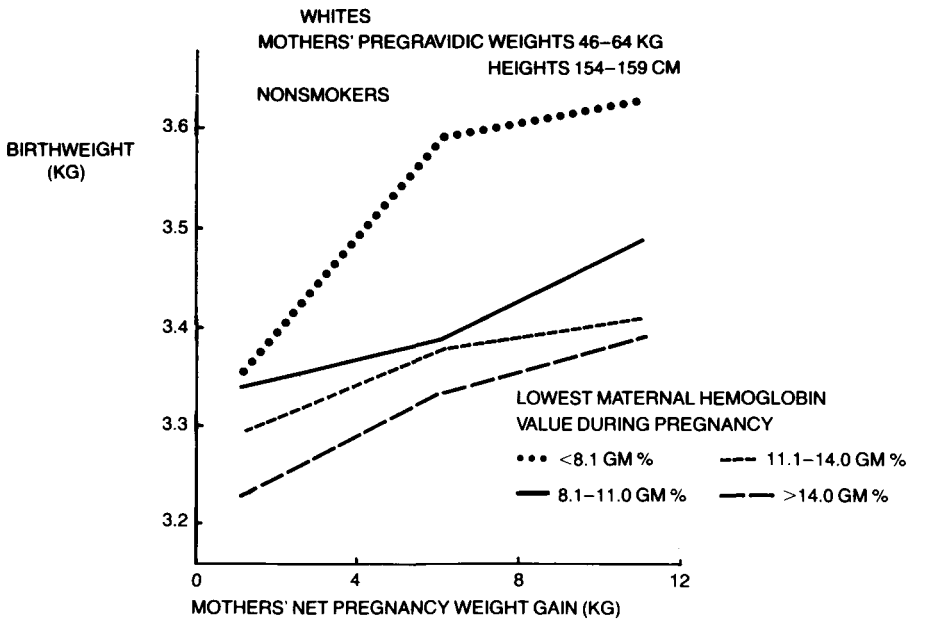

FIG. 2. Risk factors in pregnancy. (From ref. 4.)

is that the degree of anemia in the third trimester of pregnancy, which can be viewed as a consequence of hemodilution, is inversely related to birthweight (BW) (Fig. 2). The second example is that the level of peak diastolic pressure during pregnancy (up to 95 Torr), which is in some ways correlated with the circulating blood volume, is directly related to BW, even in those cases with low net maternal weight gain (Fig. 3). The presence of maternal proteinuria and/or edema did not markedly influence intrauterine growth unless peak diastolic pressure was <85 Torr. These data are substantiated by the previous work of Räihä (5) which showed a close relationship between the lack of increase of blood volume in pregnancy and incidence of prematurity. This fact suggests that IUGR in pregnancies complicated by edema, proteinuria, and hypertension can be due to reduced blood volume. Thus, therapeutic strategies aimed at expansion of plasma volume and/or amelioration of the microcirculation may be effective in at-risk mothers (6,7).

However, as recently suggested by Warshaw (8), IUGR can also be viewed from the point of view of the fetus as an adaptation in which its own size may be appropriate to the availability of nutrients, including oxygen supply. An increase in oxygen consumption has been described after chronic glucose infusion in fetal sheep (9) and in a fetus with marginal oxygen delivery this may cause increased risk. Furthermore, mothers receiving high-protein supplementation in a nutritional intervention program had an excess of prematurity and IUGR (10).

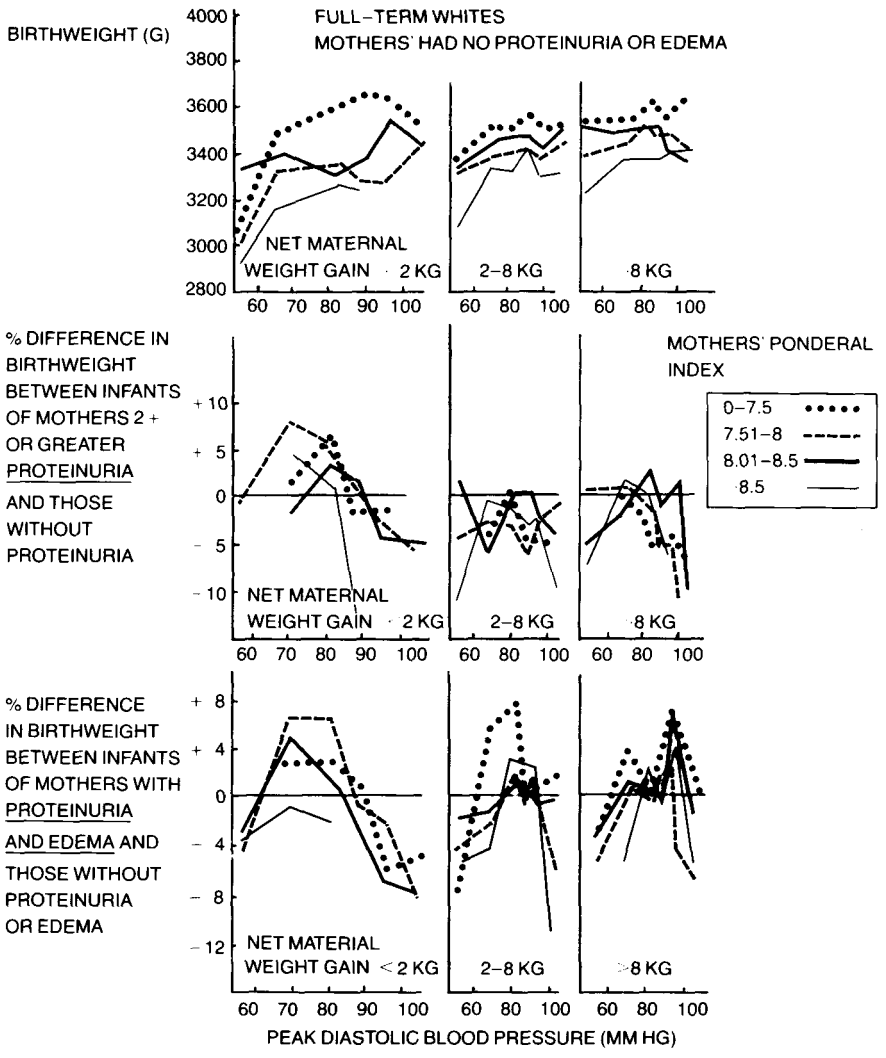

FIG. 3. Influence on birthweight of peak diastolic pressure during pregnancy. Values are referred to three classes of mothers: healthy (**top**), with proteinuria (**middle**), with proteinuria and edema (**bottom**). Values are also expressed considering mothers' ponderal index and net maternal weight gain in pregnancy. (From ref. 4.)

THE ITALIAN EXPERIENCE OR STUDY

In the Italian Perinatal Project (1973–78), the incidence of IUGR, calculated on the basis of our own intrauterine growth curves from the 32nd to the 43rd week of gestation (11–13), appeared to be 10% to 11% of all neonates, with no substantial differences between rural and industrialized areas. The causes of IUGR did not differ from those commonly recognized in other studies in well-developed countries

TABLE 1. *Risk factors for intrauterine growth*

Demographic
Age (< 17 years, > 34 years)
Unmarried
Low socioeconomic[a]
Risk condition preceding pregnancy
Low maternal weight[a]
Small stature[a]
Genital anomalies
Diseases not pregnancy-related
Nephritis
Chronic hypertension
Heart/cardiovascular disease
Liver disease
Obstetric history
Previous IUGR baby[a]
Previous preterm delivery
Previous fetal or neonatal deaths
Medical risks—current pregnancy
High parity
Multiple pregnancy
Sexually transmitted infections
Fetal anomaly
Abruptio placentae
Low diastolic blood pressure
High systolic blood pressure[a]
Toxemia[a]
Environmental risks—current pregnancy
Smoking[a]
Nutritional deprivation[a]
Heavy alcohol use
Drug abuse
Health care risk factor
Inadequate prenatal care
Evolving concepts of risk stress
Inadequate plasma volume expansion
Selected environmental pollution exposure
Selected genitourinary infections

IUGR, intrauterine growth retardation.
[a]Attributable risk values.
Adapted from ref. 19.

(Table 1) (14,15). Serious maternal diseases, especially preeclampsia, predominated as leading factors in severe IUGR. It must be pointed out that, in about 50% of infants with a BW <2,500 g, pre-existing factors (e.g., the height of both parents and the mother's pre-pregnancy weight) were responsible for a BW below the 10th percentile, though in all these cases the BW was above the 3rd percentile.

Looking at the environmental factors, it clearly appeared that heavy smoking during pregnancy was responsible for reduced BW and birth length (Tables 2 and 3), even when adjustment was made for other causes of a reduced BW, such as age and parity of the mothers and low socioeconomic status (16). These data are in the line of those reported by Naeve and Tafari (4) in the U.S.A. Perinatal Project (Fig. 4) and these authors also demonstrated that the reduced growth persists up to at least 7 years of age (Table 4).

In the U.S.A. Perinatal Project, the effect of work during pregnancy on BW was analyzed. BW was lower when women continued to work outside their homes after the 28th week of gestation than when they quit work before this time. The only exceptions were those mothers who had sit-down work and no children at home to care for (Fig. 5). Both smoking and work aggravate the risks introduced by otherwise abnormal pregnancies.

From a clinical standpoint, the major problem consists in the care of neonates with fetal growth retardation born before the 32nd week of gestation. Because of the

TABLE 2. *Influence of smoking on birthweight, head circumference, and crown-heel length*

	Nonsmokers	Stopped smoking	1–10 cigarettes / day	11 + cigarettes / day
Cases (%)	7,124 (63)	2,046 (18)	1,954 (17)	224 (2)
Birthweight (< 10th percentile) (%)	1,108 (16.0)	297 (15.0)	394 (20.8)	53 (24.2)
Odds ratios (95% int)	—	0.92 (0.80–1.06)	1.38 (1.21–1.56)	1.69 (1.23–2.32)
Odds ratios (95% int) adjusted for age, parity, socioeconomic class	—	0.90 (0.78–1.03)	1.39 (1.21–1.69)	1.73 (1.24–2.40)
Head circumference (< 10th percentile) (%)	587 (8.9)	165 (8.7)	214 (11.8)	19 (9.0)
Odds ratios (95% int)	—	0.97 (0.81–1.16)	1.37 (1.16–1.61)	1.01 (.63–1.63)
Crown-heel length (< 10th percentile) (%)	1,306 (19.8)	362 (18.9)	433 (23.8)	54 (25.6)
Odds ratios (95% int)	—	0.95 (0.83–1.08)	1.27 (1.22–1.44)	1.40 (1.02–1.91)

Sample selection: all high risk neonates, an equal number of normal neonates.

Cases are divided according to absence or presence (entity) of mothers' smoke. Numbers (and percentage) of neonates with values < 10th percentile are indicated. Significant differences from nonsmokers are underlined.

From ref. 16.

TABLE 3. *Influence of smoking on low birthweight (LBW) preterm deliveries, and perinatal deaths*

	Nonsmokers	Stopped smoking	1–10 cigarettes / day	11 + cigarettes / day
Cases (%)	7,124 (63)	2,046 (18)	1,954 (18)	224 (2)
LBW (%)	966 (13.6)	254 (12.4)	321 (16.4)	47 (21.0)
Odds ratios (95% int)	—	0.90 (0.78–1.05)	1.25 (1.09–1.44)	1.69 (1.22–2.35)
Odds ratios (95% int) adjusted for age, parity, socioeconomic class	—	0.95 (0.82–1.11)	1.35 (1.17–1.55)	1.74 (1.25–2.44)
Preterm deliveries (%)	1,077 (15.1)	287 (14.0)	258 (13.2)	38 (17.0)
Odds ratios (95% int)	—	0.92 (0.77–1.18)	.85 (0.74–0.99)	1.15 (0.80–1.64)
Perinatal deaths (%)	263 (3.7)	68 (3.3)	70 (3.6)	4 (1.8)
Odds ratios (95% int)	—	90 (0.68–1.18)	.97 (0.74–1.27)	0.47 (0.17–1.28)

Sample selection: all high risk neonates, an equal number of normal neonates.

Cases are divided according to absence or presence (entity) of mothers' smoke. Significant differences from non-smokers are underlined.

From ref. 16.

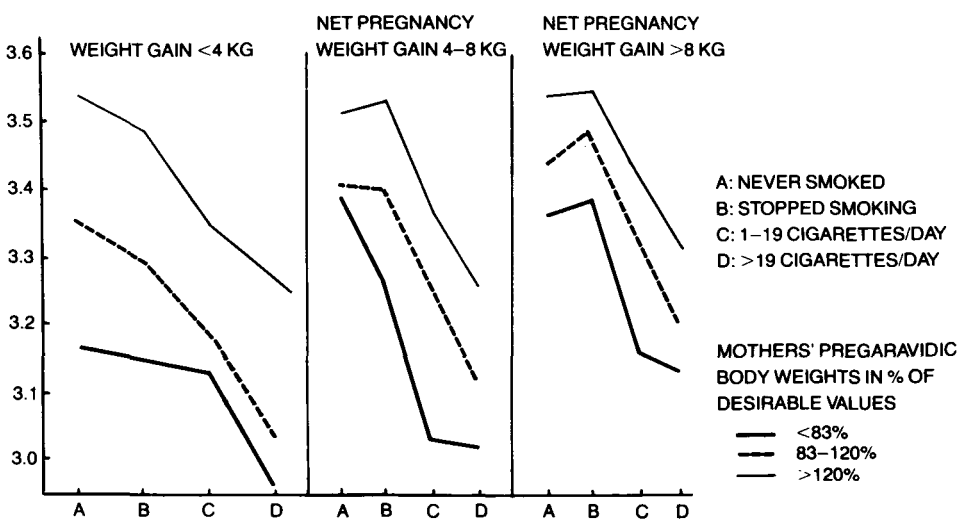

FIG. 4. Influence of tobacco smoking on birthweight. Values are expressed according to the entity of smoke (**A,B,C,D**), to mothers' pregravidic nutritional status and to net maternal weight gain in pregnancy. (From ref. 4.)

TABLE 4. *Intrapair comparisons of full-term siblings whose mothers smoked in one but not the other of their pregnancies*

	Birth	7 years of age	No. pairs of siblings
Body weights			
Stopped smoking	3,341 ± 440 g	24.3 ± 4.6 kg	140
Continued smoking	2,898[c] ± 384 g	22.9[c] ± 3.1 kg	
Body lengths			
Stopped smoking	50.9 ± 2.2 cm	121.2 ± 5.0 cm	
Continued smoking	50.3[a] ± 2.4 cm	119.5[c] ± 4.6 cm	
Head circumferences			
Stopped smoking	34.4 ± 1.2 cm	51.6 ± 1.3 cm	
Continued smoking	33.8[c] ± 1.3 cm	51.4 ± 1.4 cm	
Placental weights			
Stopped smoking	458 ± 88 g		
Continued smoking	431[b] ± 84 g		

All values ± 1 SD. [a]$p < 0.02$ compared with value in stopped-smoking category; [b]$p < 0.01$; [c]$p < 0.001$.
From ref. 4.

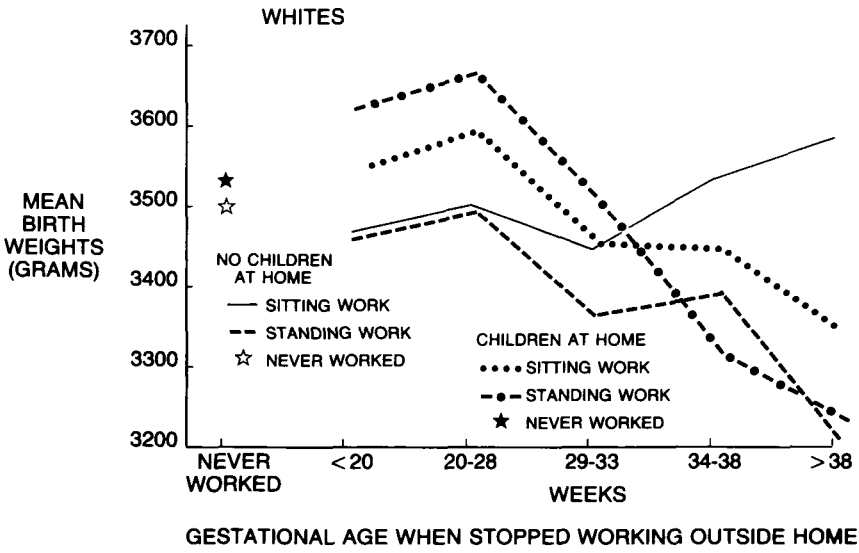

FIG. 5. Influence of work during pregnancy on birthweight. Data are analyzed according to type of work (sitting or standing) and presence or absence of other children at home to care for. (Data from ref. 4.)

TABLE 5. *Mean birthweight of liveborn infants from the whole population (WP) compared with interventive deliveries (ID)*

	Gestation (weeks)				
	27	28	29	30	31
WP[a]	1,047	1,119	1,360	1,516	1,702
ID[a]	647	846	904	1,123	1,257
WP[b]	1,022	1,162	1,242	1,382	1,551
ID[b]	1,018	1,077	1,150	1,280	1,458

[a]Data from ref. 18.
[b]Data from ref. 17.

relative lack of accurate intrauterine growth curves below this gestational age, it is not easy to define IUGR in such infants. Only recently have two reports (17,18) provided data on "normal" growth for babies born highly preterm, and what is more, the data offered in these studies do not entirely coincide (Table 5). However, it appears clear that after subtracting those babies suspected of being sick *in utero* and born with an "interventive" delivery, precise intrauterine growth curves can be drawn, which then become a useful tool to classify IUGR in the very preterm group. Furthermore, considering that IUGR seldom appears before the 24th week of gestation and that early ultrasound evaluation of gestational age is highly reliable, we shall in the near future be able to define IUGR accurately in babies born from the 25th to 32nd week of gestation (Figs. 6–8).

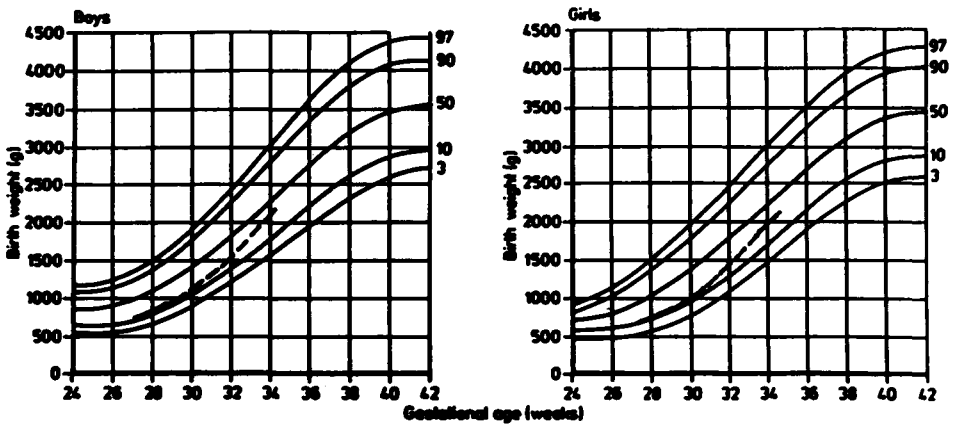

FIG. 6. Mean values *(broken line)* for birthweight in babies born after interventive delivery from 27 to 34 weeks of gestation (cesarean section or induction of labor for maternal or fetal-intrauterine growth retardation causes). Birthweight centiles for all the babies studied are also shown. (From ref. 18.)

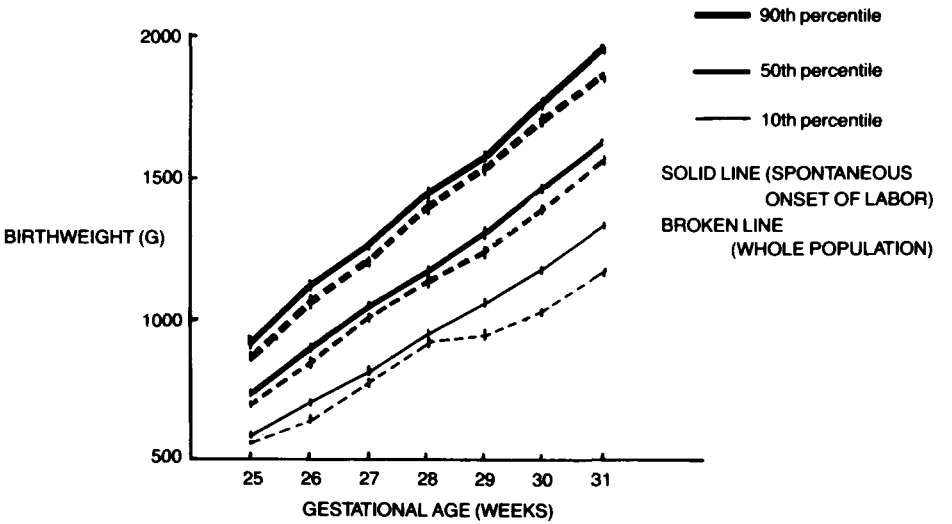

FIG. 7. 10th, 50th, 90th percentiles (not smoothed) for birthweight between 25 and 31 weeks gestation (whole population and spontaneous onset of labor). (From ref. 17.)

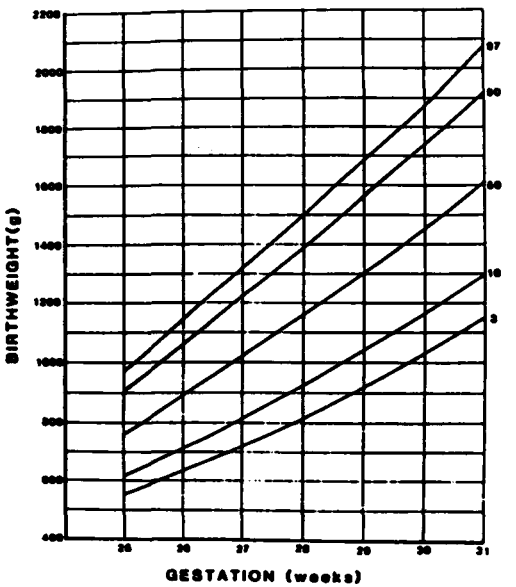

FIG. 8. Smoothed birthweight centile chart for infants 25 to 31 weeks gestation delivered spontaneously (i.e., excluding "interventive" deliveries). (From ref. 17.)

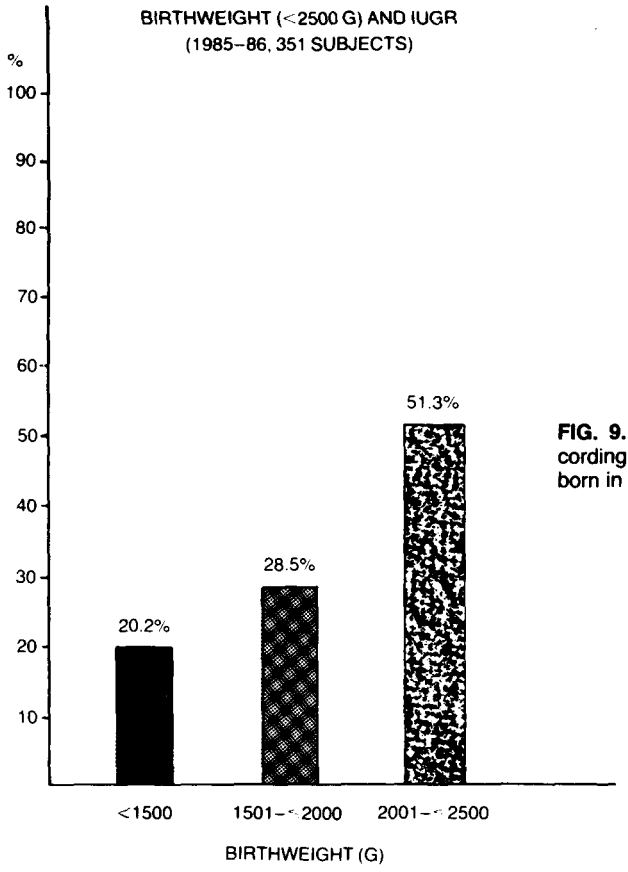

FIG. 9. Percentage distribution according to birthweight of IUGR babies born in our institution (1985–86).

With this background, we have recently reviewed etiological factors in a group of IUGR babies of BW <2,500 g, born in our institute in the last two years. Of 1,218 low birthweight (LBW) neonates, there were 351 cases of IUGR (31%).

Percentage distribution according to birthweight and gestational age is illustrated in Figs. 9 and 10. Analysis of etiological factors, subdivided into maternal, fetal, placental, and unknown reasons, indicates the following (see Table 6, Fig. 11): (a) In the great majority of cases, it is possible to find a cause for IUGR; (b) maternal factors predominate in babies born with a BW <1,500 g; (c) preeclampsia is the leading cause of IUGR in babies born with BW <2,000 g; (d) maternal environmental factors (smoking, drug abuse) predominate in babies with a BW >2,000 g; (e) placental factors are almost equally distributed in these 3 categories of BW; (f) infections are scarcely represented, which contrasts with the previous findings of Naeye and Peters (19) but is in accord with more recent findings (20); (g) twinning, especially monozygous, is a leading cause among fetal factors; and (h) serious mal-

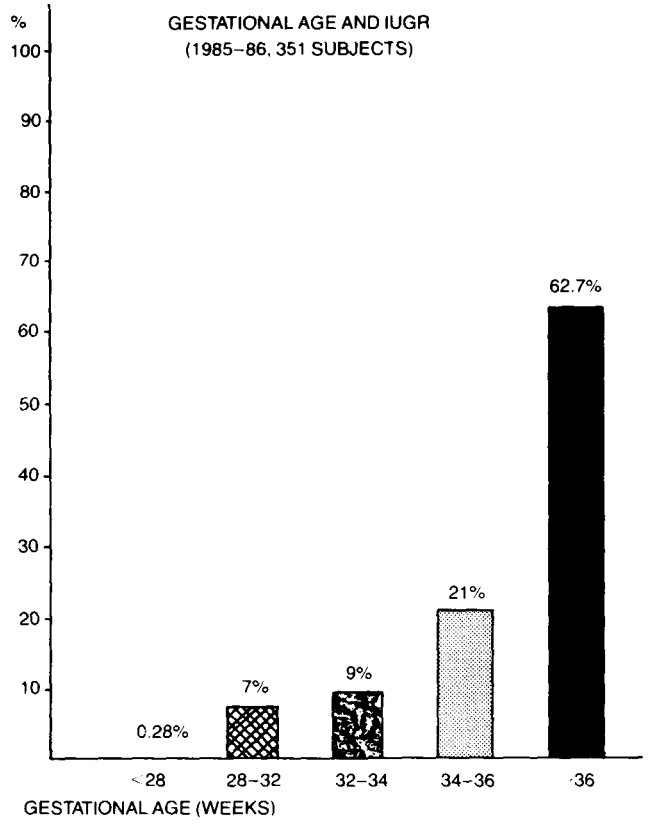

FIG. 10. Percentage distribution according to gestational age of IUGR babies born in our institution (1985–86).

TABLE 6. *Etiological factors for intrauterine growth retardation (IUGR)*

Maternal	Placental	Fetal
Cardiovascular	Small	Malformation
Infections	Abnormalities	Infections
Increase in weight (≤ 6 kg)		Chromosome abnormalities
Smoking (> 10 cigarettes / day)		Twinning
Alcohol		
Drug addiction		

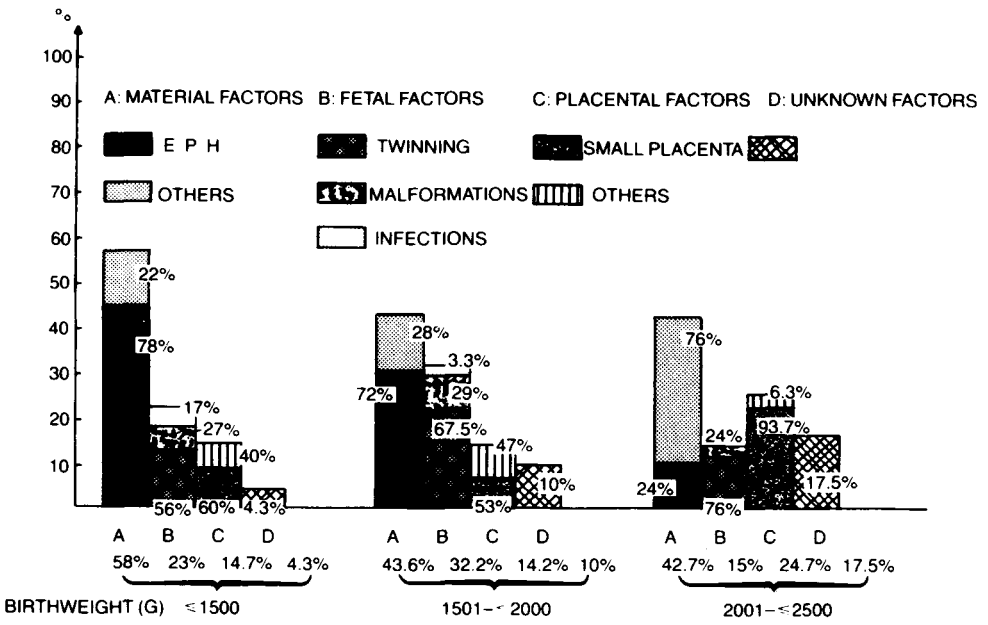

FIG. 11. Percentage distribution of causes of IUGR babies born in our institution (1985–86).

formations, because of early intrauterine diagnosis followed by abortion, are rarely observed. Analysis of the ratio of placental weight to BW did not discriminate among the various etiological factors, agreement with earlier data of Molteni, Stys, and Battaglia (21).

If we take our findings as an indication of the causes of severe IUGR in a well-developed country with adequate antenatal care, and accept that maternal vascular factors together with placental abnormalities are the major causes of IUGR, then we may suggest that interventions aimed at cardiovascular control can be highly recommended. There is evidence that the evaluation and correction of abnormalities of plasma volume during pregnancy (6) and the early screening of pregnant women with a tendency to microvascular lesions (22) can be effective in reducing IUGR.

Obviously, another area of medical intervention is the prevention of infectious diseases, especially of the genito-urinary tract, because these can play a considerable role as causes of preterm delivery (19).

It has recently been pointed out (23) (Fig. 12) that abnormalities of glucose metabolism in pregnancy, leading to a tendency to hypoglycemia and to a lower release of insulin after glucose challenge, may be associated with some cases of IUGR. We do not yet know if this relationship is concomitant or causative. If the latter is true, we may expect that treatment causing increased plasma glucose levels in pregnancy would ameliorate growth failure associated with such abnormalities of glucose metabolism. However, experimental studies (9,24) and some clinical trials have not

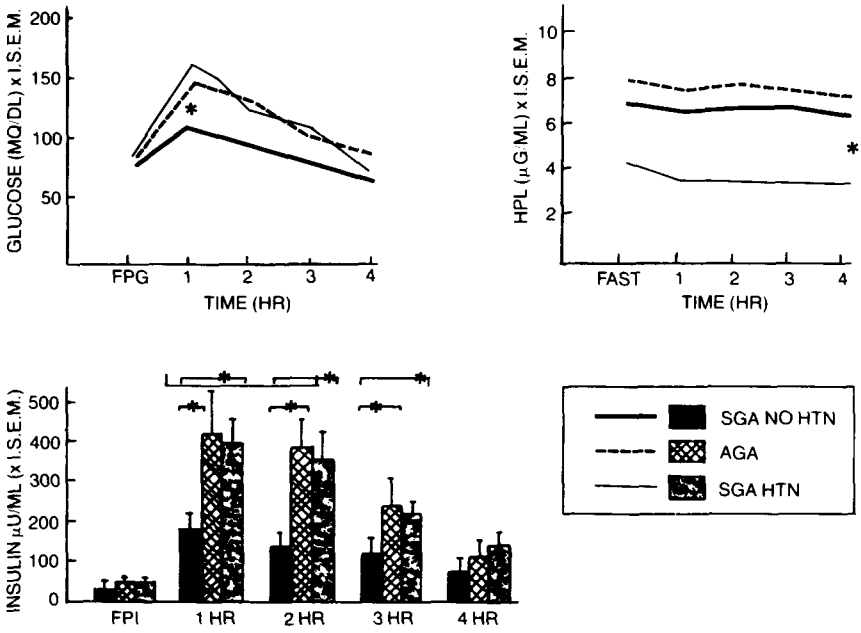

FIG. 12. Distribution of plasma glucose, human placental lactogen, and insulin levels after oral glucose load (OGL). HTN, Hypertensive; SGA, small for gestational age; AGA, appropriate for gestational age (*$p<0.05$). (From ref. 23.)

been very effective, indicating that the increased supply of nutrients to the fetus must be coupled with an adequate oxygen delivery.

Socio-economic factors, including smoking and drug abuse, can be counteracted efficiently only by a more general approach to health care supported by wise politicians.

At the present time, we feel that in order to improve the long-term prognosis of IUGR babies (25), extremely careful monitoring during pregnancy, labor, and delivery is mandatory, since the affected fetus tolerates stressful conditions poorly. Good perinatal support, including efficient neonatal care given by qualified neonatologists, can minimize the long-term ill effects which have too often been described in the past.

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