0029-7828/82/3708-0499/$2.00/0
OBSTETRICAL AND GYNECOLOGICAL SURVEY Vol. 37, No. 8
Printed in U.S.A.

review

The Timing Factor in the Pathophysiology of the Intrauterine Growth Retardation Syndrome

JOSÉ VILLAR[1] and JOSÉ M. BELIZAN[2]

Department of Maternal and Child Health, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland,[1] and the Institute of Nutrition of Central America and Panama (INCAP), Guatemala, Central America[2]

Three different types of intrauterine growth retardation can be identified depending on the moment at which supplies to the fetus are diminished. When a reduction in sustenance occurs early in the first trimester of pregnancy, a well-proportioned but growth-retarded baby may be expected. When the negative factors develop around the 30th week of pregnancy, the result is a disproportionately growth-retarded infant. Both types of retardation can be illustrated using longitudinal uterine height and biparietal diameter values and by neonatal anthropometry. Epidemiological examples exist defining factors which produce these two kinds of retardation. The third type occurs when a reduction in food supplies takes place in the last month of pregnancy and causes a depletion of the fetal fat stored. Weight retardation is observed with little or no height impairment. In planning public health activities such as nutritional interventions for developing countries, the type of intrauterine growth retardation present in the target population should be considered in order to determine which type of intervention would be most appropriate, and establish its correct timing.

Low birth weight infants constitute a major public health problem, especially in developing countries. During 1975, 21.9 million low birth weight (LBW) infants were born throughout the world and 93 per cent of those births took place in less developed areas (12). It is now well accepted that among LBW babies there are two different groups: premature infants, those babies which are born early (before 37 weeks of gestation) but whose weight is above the tenth percentile for gestational age; and those whose weight at birth, for various reasons, is low for their gestational age, regardless of whether they are born prematurely, at term or post-term. We also know by now that the proportion of these two kinds of newborns is not fixed in a given population, but changes in relation to the overall incidence of LBW: the higher the incidence of LBW, the greater the proportion of intrauterine growth-retarded (IUGR) infants, while the number of prematures remains relatively constant (1).

Recently, it has been reported through the use of several different methods of diagnosis that the IUGR group is not a homogenous one and that the etiology of such retardation, as well as the future development of these babies, can vary. Rosso and Winick (22) have thoroughly reported on etiological classification; thus, it need not be discussed further here. This article will focus on the fact that, independent of the characteristics of the factor or disease (e.g., malnutrition) which affects intrauterine growth in newborns without congenital malformations, the time at which the insult occurs is the critical element which will give the newborn its physical characteristics. From this is derived a clinical classification of IUGR infants.

Normal Intrauterine Growth

For obvious reasons, there are no longitudinal intrauterine growth standards. Nevertheless, there are many cross-sectional standards that can be used to assess "normal" growth. As early as 1920,

Reprint requests to: José Villar, M.D., Department of Maternal and Child Health, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, MD 21205.

Dr. Belizan's present address: Centro Rosarino de Estudios Perinatale (CREP), Rosario, Argentina.

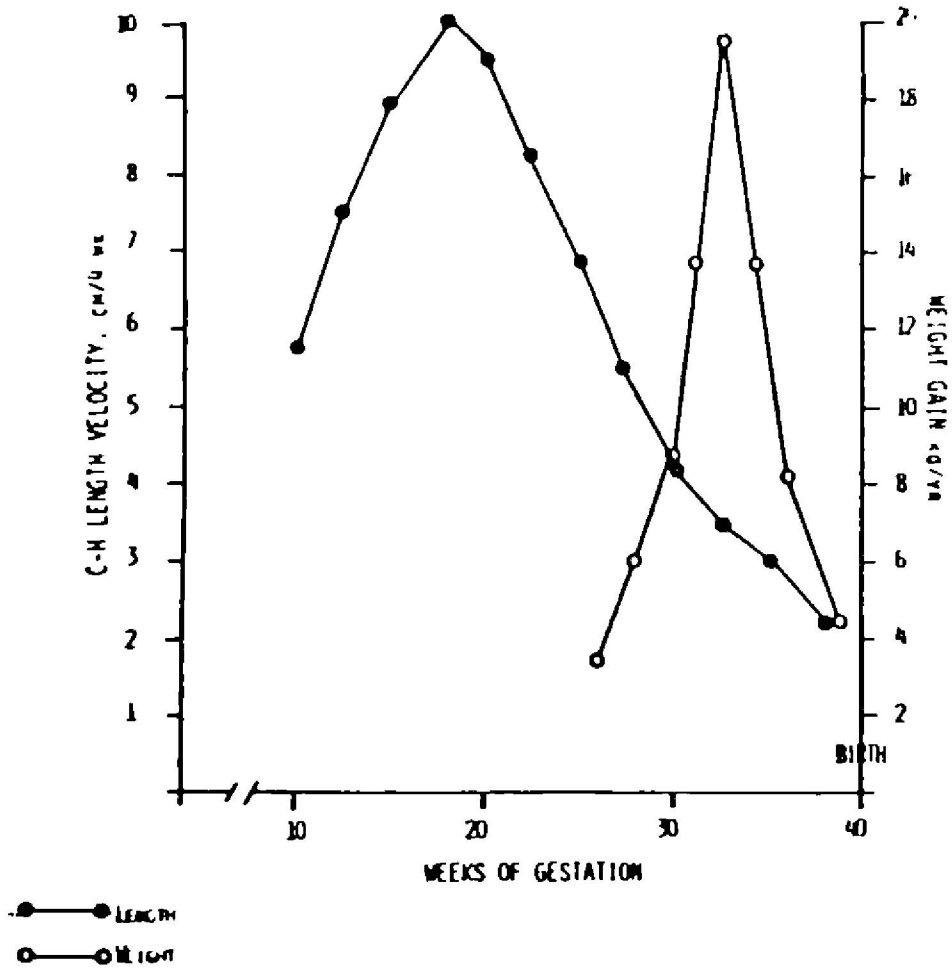

Fig. 1. Velocity curves for length (*closed circles*) and weight (*open circles*) in the prenatal period. (Adapted from Tanner (24).)

Streeter (23) published velocity data for weight and sitting height. Recently, Tanner (24) has reported velocity curves for weight and crown-heel length in the prenatal period as shown in Figure 1. As can be seen, the characteristics of both velocity curves are quite similar, the only difference being the time at which the growth peak occurs.

The peak in the velocity of length growth occurs first, around the 20th week (for sitting height the peak is at the 16th week (23)), while weight increase shows its maximum value at about 33 weeks of pregnancy. The latter is a consequence of the timing of fat deposition. At about 26 weeks, fat represents only 1 per cent of total fetal body composition (10 g). Thereafter fat accumulation proceeds until it reaches 12 per cent of total weight or 360 g at 38 weeks (27). Therefore, while length growth peaks during the second trimester, weight growth is predominantly a phenomenon of the third trimester.

Greenwald's data (8) on body weight and length, placental, and organ weight support this growth pattern. Using his information, we were able to calculate the percentage of total weight and length at term reached at each week of gestation. As Figure 2 shows, by the 28th week, length has reached 71 per cent of the mean length at term (41 weeks), while weight was only 32 per cent of the full-term infant weight. This is coincident with the expected growth calculated from Tanner's data (Fig. 1)

Hypothesis: An IUGR Classification

Considering these growth characteristics, it can be speculated that differences in the timing of the periods at which the fetus is negatively affected will produce different patterns of alterations of normal growth. For example, nutritional deficiencies, smoking, infections or vascular alterations which result in a reduction of the placental blood flow during the first trimester of gestation will produce alterations in length, as well as in weight. Alternatively, if the insult begins around the 27–30th week of gestation, it will result in weight retardation, but less damage will be evident in length growth. In the same way, if the loss occurs after the 35–36th week of gestation, when velocity of growth for both length and weight has decreased, the fetus will have to use its own fat stores during the next weeks, resulting in weight loss, but not a decrease in length.

With the above considerations, three clinical types of IUGR can be considered: Type I would include all those newborns who did not receive enough nutrients dating from the first trimester and continuing throughout the remainder of the gestational period. This group will be called chronic or proportionate IUGR. Type II would consist of newborns whose growth was adversely affected by a process starting some time between the 27th and 30th weeks of gestation. These fetuses grew in length during the second trimester, but the growth process was not completed since the inception of the adverse effect occurred prior to the time the fetus was to reach its peak velocity in weight growth. Figure 1 gives a graphic representation of this time relation. It also shows that most of the length growth was accomplished in these cases. Weight growth, however, will have been affected throughout the period of maximum fetal weight gain and, therefore, severely compromised. This type will be called subacute or disproportionate IUGR.

To the third type would belong those fetuses who underwent normal intrauterine growth processes, but were negatively affected in the last 2 or 3 weeks of gestation when growth in length and weight are almost completed. In the absence of adequate supplies, these fetuses had to utilize their own fat

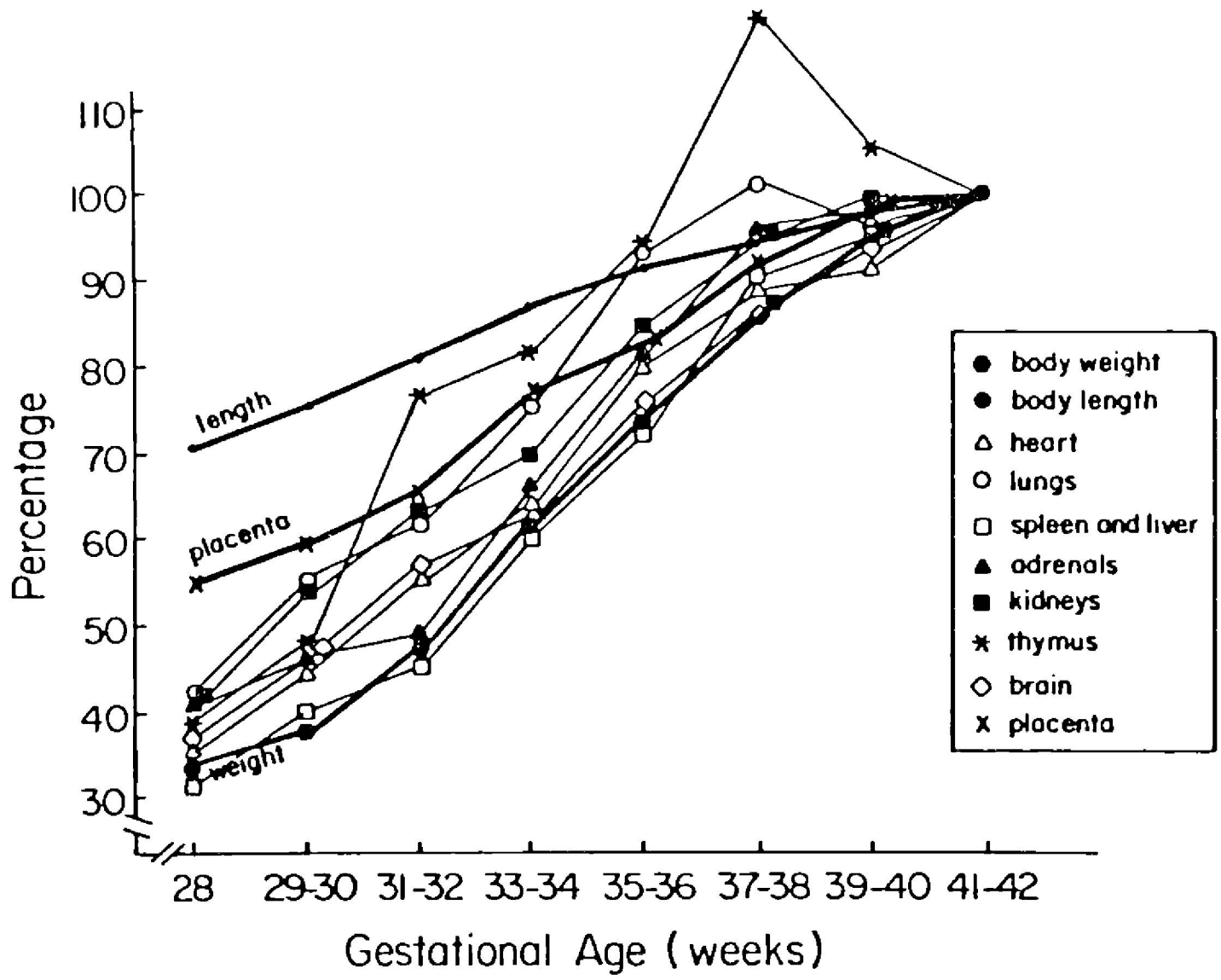

Fig. 2. Percentage of weight of body weight and length, placental and organ weight of the total weight, and length at term by week of gestation. Only newborns with a birth weight within 1 SD from the mean for respective week of gestation were included. (Adapted from data reported by Gruenwald (8).)

stores and, therefore, weight losses ensued. Type III will be called acute IUGR.

Skin fold measurements taken at birth may be utilized to differentiate Types II and III. However, given that fat is not the only component of fetal weight gain during the last trimester, this kind of measurement can discriminate to some degree only. Type III should have very low fat but relatively normal muscular mass, while Type II should show reductions in both muscle and fat.

Naturally, this classification is arbitrary to a degree. It is of necessity based on artificial divisions imposed upon a phenomenon whose inception can occur at any point during the course of the pregnancy. Nevertheless, it is intended to be an instrument whereby that event it attempts to categorize can be better understood.

In what follows, we present some evidence from the literature which may confirm the existence of these three different growth patterns, and can help us understand how they come about. All these examples use the Ponderal Index (PI)[1] as defined by Rohrer (21) to describe the relationship between weight and length. When the PI was not available for a given population, it was substituted by Miller's distribution by percentile groups according to fetal age (16).

[1] $\frac{\text{Weight in grams}}{(\text{length in cm})^3} \times 100$.

Type I

Clinical Presentation

Figure 3A shows the development of biparietal diameter measurements (BPD) from as early as 19 weeks of gestation until birth. As can be seen, the values are always below the tenth percentile for their corresponding gestational ages. This pattern of growth was previously described by Campbell as "low profile" (4).

As has been shown recently (3), the systematic measurement of uterine height can be effectively used as a clinical indicator of growth retardation. Figure 3B presents an example of one case of fetal growth which was followed by this method (2). Uterine height values were below the 10th percentile during almost the entire gestational period, and at birth the infant's weight was 2650 g, its length 45 cm, and weight/length^3 ratio was 2.9. This value

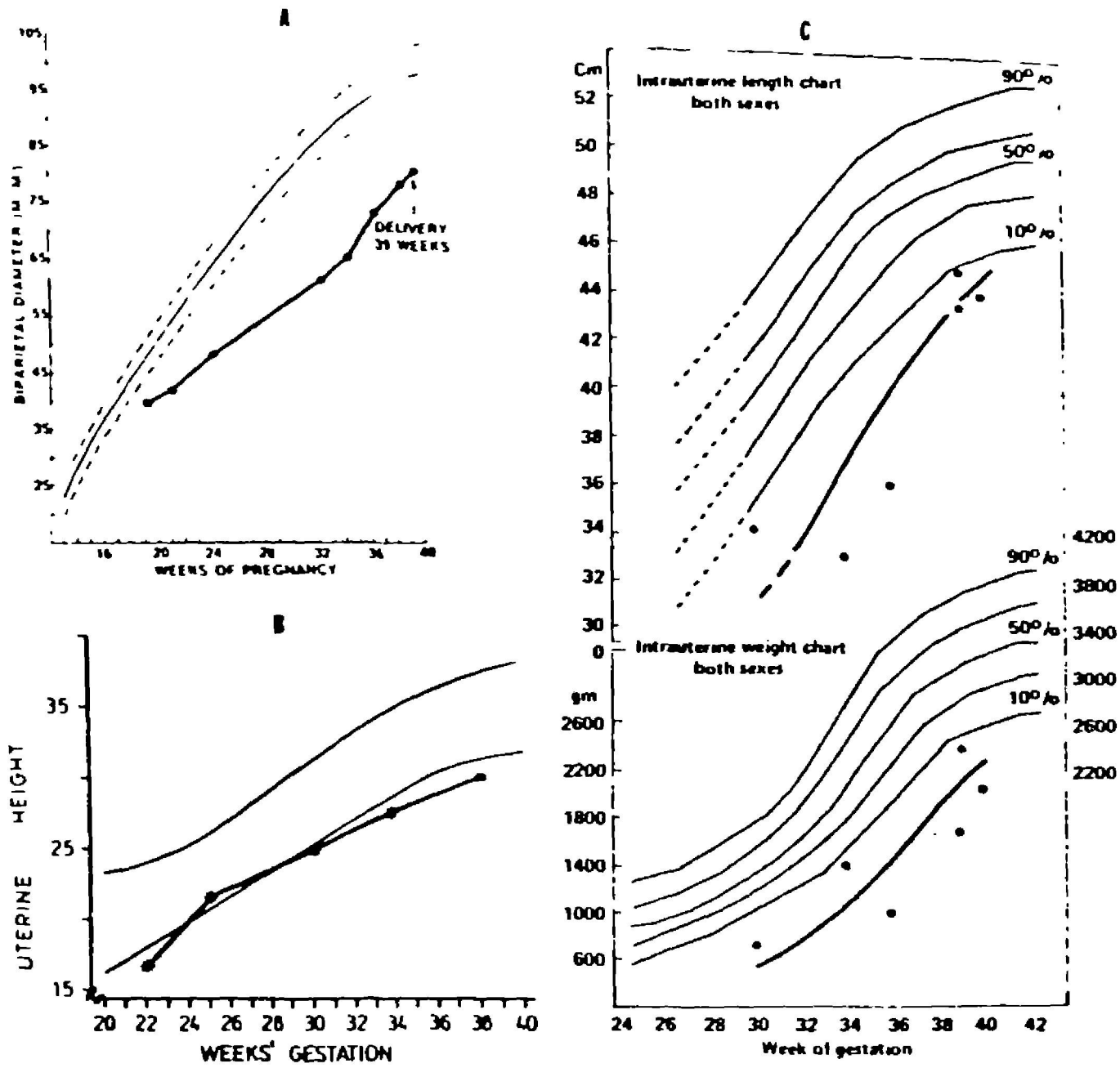

Fig. 3. Development of biparietal diameter (A) (10), uterine height (B) (2), and clinical assessment at birth (C) (26) in intrauterine growth-retarded babies. The values are always below the corresponding 10th percentile. For example, delivery took place at the 39th week of gestation (A) in the monitored infants with biparietal diameter and the newborn weight 1.78 kg (10). The uterine height case (B) born at the 38th week of gestation weighed 2.65 kg, its length was 45 cm, and the weight/length^3 ratio was 2.9 (2) (proportionate growth retardation).

falls between the 90th and 97th percentile according to both Miller's standard and that reported for a similar population by Guayasamin et al. (9). In the above case, both weight and length were affected, resulting in proportionate growth retardation.

Urrusti et al. (26) reported six cases of intrauterine growth retardation (IUGR) where, again, both weight and length were below the 10th percentile of standard values (Fig. 3C). As a consequence of this double retardation, these cases obtained ponderal index values which were within the normal range for their gestational age (13, 14). Urrusti's cases all exhibited the three characteristics which were proposed above as being associated with Type I IUGR: weight and length values below the 10th percentile but normal ponderal index values. From the analysis of this figure, they concluded that proportionate growth retardation may begin prior to the 28th week of gestation. From data obtained from uterine height measurements (2, 10) and biparietal diameters (10, 14) (Fig. 3, A and B), cases of proportionate IUGR show values below the 10th percentile before the 20th week of amenorrhea, demonstrating that this growth failure is produced and can be diagnosed before this gestational age.

Epidemiological Studies

In order to prove the above points using population models, it becomes necessary to trace, in a given population, factors that appear at specified periods during the course of pregnancy and which have recognized adverse effects on fetal growth. Let us begin by examining factors which could be present in the study population from the inception of pregnancy or earlier. Two such factors are the presence of chronic severe maternal malnutrition and the existence of regular smokers in the pregnant population.

Recently, Mata (15) has reported the results of a

longitudinal study in a rural area of Guatemala. A cohort of 415 women with chronic severe malnutrition was followed during their gestations. In this population, maternal height and weight were significantly associated with the infant's anthropometric measurements. The incidence of newborns weighing less than 2500 g who were IUGR was 34 per cent (143/415) and the mean birth weight for these infants was 2366 ± 15 g; the mean height was 43.5 ± 0.1 cm. Both values are below the 10th percentile of the standard of well-nourished Guatemalan populations. Nevertheless, the mean weight/length^3 ratio was 2.54, a value that falls around the 50th percentile in all the curves available (16, 14). Further, in a population of underweight women in the United States defined as 10 per cent or more below standard weight for height, a significant increase in the proportion of infants below the 25th percentile for weight and length was found (7). However, the difference was not significant when the weight and length were correlated: the proportion of infants with ponderal index below the 25th percentile was 26 per cent for the cases and 24 per cent for the normal controls. The authors concluded that these infants were "proportionately small." In short, a factor that affects fetal growth, when present from the beginning of gestation, affects weight and length proportionately, producing infants with a normal ponderal index. The second factor that we will discuss is the effect that smoking from the inception of pregnancy has on the incidence of proportionate IUGR. Miller (17) has studied this effect on Type I IUGR newborns, calling them "short for date." He included in the study only mothers with single totally uncomplicated pregnancies and infants without intrauterine infections or congenital malformations. From this data we were able to calculate that smoking mothers have a 5-fold increased risk of having a "short for date" infant than nonsmokers, after controlling for weight gain during pregnancy (odds ratio 4.49, 95 per cent, confidence interval 2.08–9.69). The same effect was present in both "low weight gain" and "great weight gain" mothers (odds ratios 4.6, 4.45). In the same vein, Davies (6) found a decrease in birth weights among 1159 infants whose mothers' smoking habits were ascertained early in pregnancy; moreover, when those infants were measured at 7 to 14 days of age, a similar reduction in body length and head circumference was noted. The recent report on smoking and health by the U.S. Surgeon General (25) concluded: "Smokers' babies are short for dates as well as light and do not exhibit reduction in ponderal index."

Type II

Clinical Presentation

An example of this second type of IUGR was reported by Gruenwald (8) and is presented in Table I. Two cases of IUGR (Case 1 and 2) full-term infants exhibited patterns almost identical to that of a normal infant weighing 1750 g at 32 weeks of gestation. It could be concluded from this that both IUGR cases were affected by some factor which stopped their growth at the 32nd week of gestation. According to our hypotheses, an insult affecting fetal growth at this gestational age should produce a severe reduction in weight but have less effect on length. That is, in fact, what occurred in these two cases and it can be demonstrated by comparing them with a normal newborn with 38 weeks of gestation. From Table I, it can be calculated that weight was severely affected with the infant at 59 per cent of its theoretical weight. Length, as we presumed, was less affected as the two cases achieved 90 per cent of the length for the normal control case. The weight/length^3 for both IUGR newborns are also presented. As the hypothesis predicts, they are low for 38 weeks (2.1, 2.2) and fall below the 10th percentile of both Miller's (16) and Lubchenco's (14) PI standards for this gestational age.

Figure 4 shows the growth patterns reported for disproportionate growth retardation. When monitored with ultrasound, Figure 4 shows that biparietal diameter increments are normal until the 28th week of gestation, at which point the curve begins to dip toward the 10th percentile (10). Figure 4B shows growth patterns as detected by measure-

TABLE 1 **Weight and lengths of two severely growth-retarded neonates compared with normal values for their gestational age and birth weight (8)**

	Normal standard for 38 weeks	Case I	Case II	Normal Standard for 1750 g
Gestational age	**38**	**38**	**39**	**32**
Body weight (g)	3050	1795	1800	1750
Crown-heel length (cm)	50	44	44	43
Weight/length^3 × 100	2.4	2.1	2.2	2.2

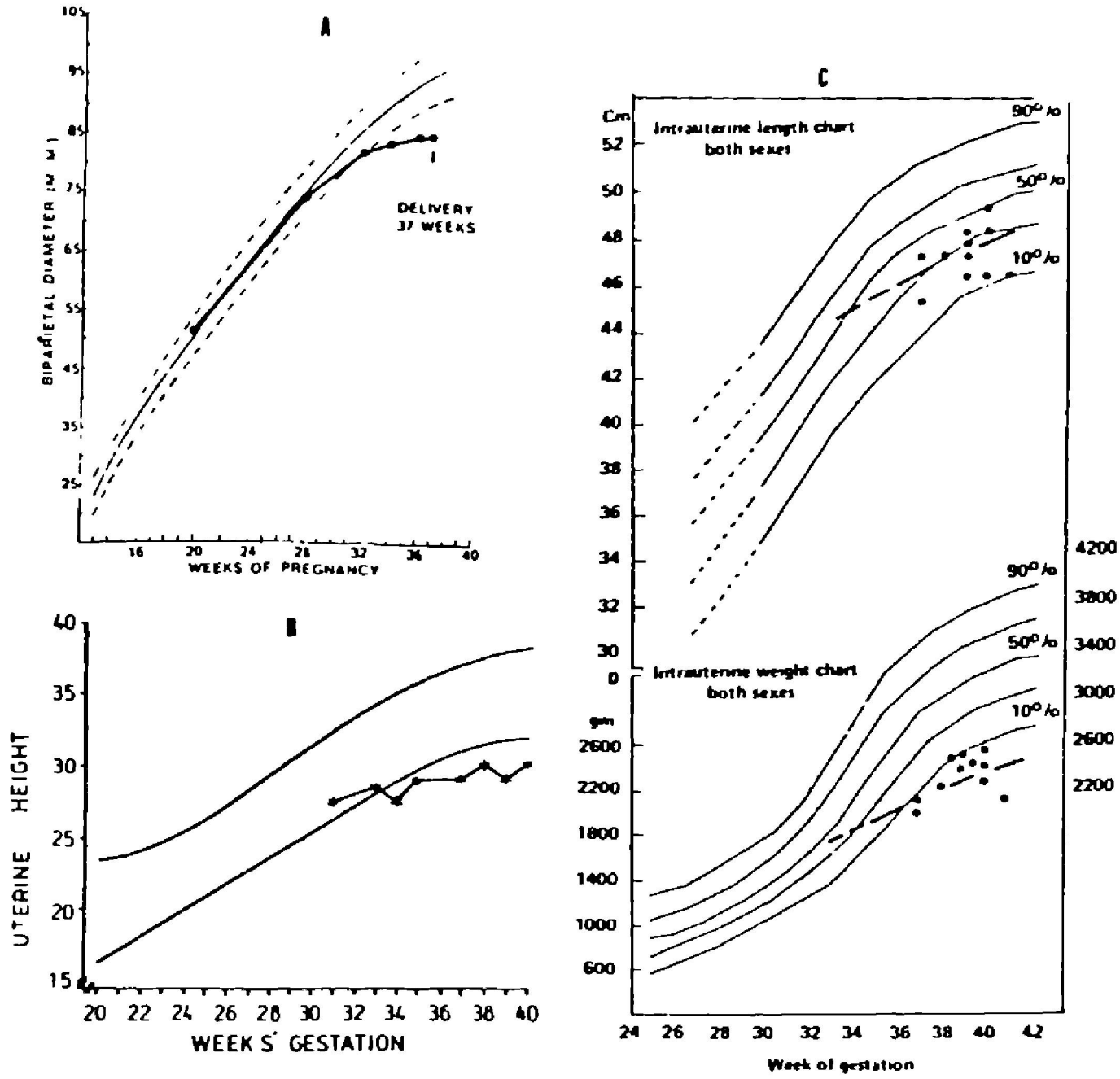

Fig. 4. Development of biparietal diameter (A) (10), uterine height (B) (2), and clinical assessment at birth (C) (26) in intrauterine growth retarded babies. At the beginning of pregnancy the values are, in A and B, within normal limits, but around the 33rd week of gestation they fall below the 10th percentile. In the pregnancy followed with biparietal diameter, delivery took place at the 37th week of gestation and the newborn weighed 1.53 kg (10) (A). The uterine case born during the 41st week of gestation weighed 2.25 kg, its length was 47 cm, and the weight/length^3 ratio was 2.17 (2) (disproportionate growth retardation).

ments of uterine height. As in the previous figure, one can see that they fall below the 10th percentile after the 33rd week of gestation. The newborn's weight was under 2250 g, its length was 47 cm, and the length of the gestational period was 41 weeks as established by both the clinical method and the date of the last menstrual period. The weight/length^3 ratio was again low (2.17), showing disproportionate growth retardation (2).

Figure 4C plots the values of birth weight and length for 11 infants reported by Urrusti et al. (26) as having disproportionate growth retardation. Length growth was almost unaffected, whereas the values for weight are all below the 10th percentile. All these infants had low weight/length^3 ratios which fell around the 10th percentile of Lubchenco's standards (14).

Urrusti et al. (26) have proposed that the disproportionate type of IUGR begins in the 34th or 36th week of gestation. However, based on ultrasound and uterine height evidence, it seems that retardation appears before that time. In the uterine height series, nine cases were reported as having values that had already fallen below the 10th percentile by the 32nd and 34th weeks of gestation (2). Moreover, the ultrasound example shows that the values were below the normal limits from the 32nd week on. If we go back to the velocity curves, we can see that a process which considerably affects weight increase has to begin during the period which starts at week 30, when the velocity of weight gain begins to increase (Fig. 1). As for length growth, it was previously postulated that in Type II IUGR it is affected, but not as critically as weight increase. This "moderate" retardation in length growth should occur at least around the 30th week of gestation, which is when the velocity of growth for length begins to be minimal.

Epidemiological Studies

Two factors have been reported to be associated with disproportionate growth retardation. As was suggested, both should affect the fetus during the last trimester. Miller et al. (17) found that relatively well-nourished women with low weight gain during pregnancy had a significantly higher incidence of "low PI infants." Miller (16) had previously found an incidence of preeclampsia of 24.2 per cent in mothers of disproportionate growth-retarded infants, significantly higher than the 6 per cent found among mothers of normal newborns. It is interesting to note that in this series both mean weight and length were significantly different from the corresponding values in the control group and the value of the mean ponderal index was 2.09 ± 0.08, below the 10th percentile of Miller's standards.

Type III

Clinical Presentation

This group included those babies who were insulted during the last month of gestation. In this case, length should not have been affected, but the weight should be reduced, producing relatively long, thin babies.

Figure 5 presents a case that shows this acute affect. The development of biparietal diameter was normal during the course of gestation, but with a small deviation from the 50th percentile by the 34th week of gestation. As was pointed out previously, by the 33–34th week, the length growth period is almost totally completed and only weight can be affected. In this case, biparietal diameter growth was slightly retarded. The product of this pregnancy was a 36-week newborn with a weight of 1970 g, a value below the 10th percentile for that gestational age for this population, with fully normal length (50 cm), producing a very low ponderal index of 1.50 (20).

Epidemiological Evidence

Classic examples of this are the post-mature infant of the baby born of a mother with severe acute preeclampsia. In a series of pregnancies with gestational age confirmed, those who were born after 43 weeks had a 3 per cent reduction in body weight compared to neonates born between the 42–43rd weeks. The reduction in height was only 0.4 per cent (13). Curbelo (5) describes 150 newborns from acute preeclampsia pregnancies and compared their measurements with the standard values

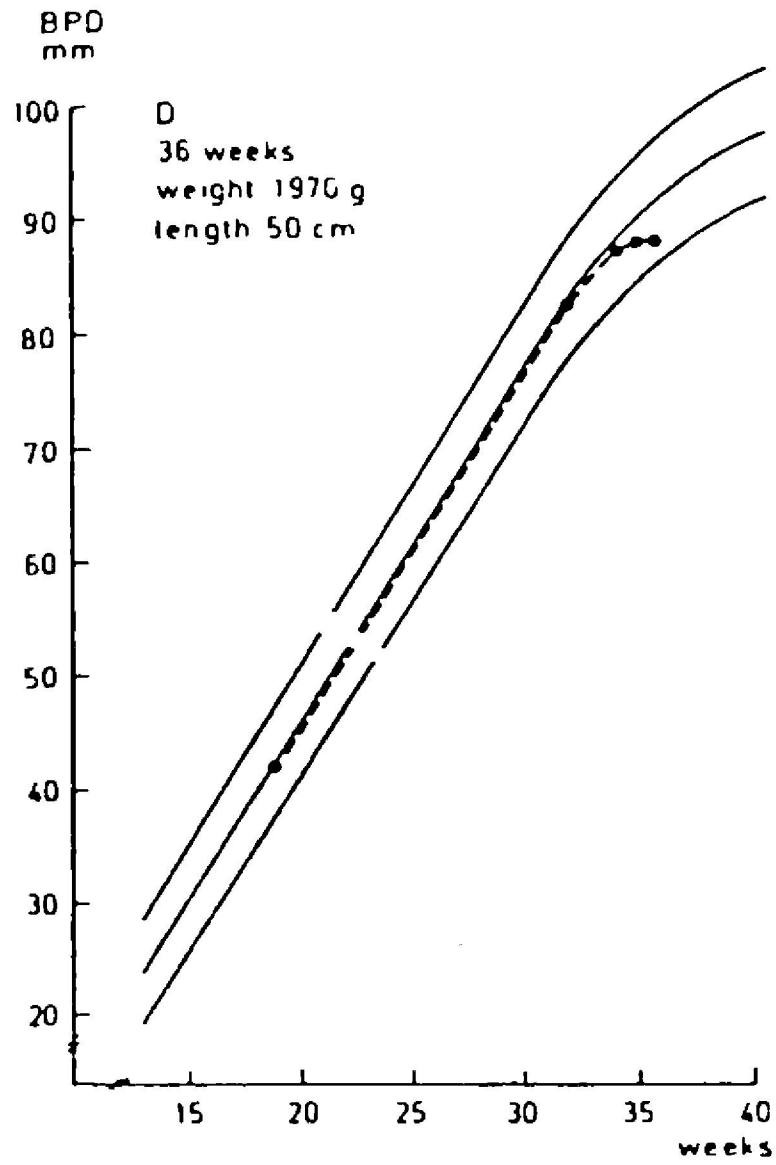

Fig. 5. Development of biparietal diameter in an intrauterine growth-retarded baby. The values were normal during the course of the gestation, but with small deviation from the 50th percentile by the 34th week of gestation. Delivery took place at 36 weeks and the newborn weighed 1970 g, its length was 50 cm, and the weight/length^3 ratio was 1.50 (20).

for that population. The probability of low birth weight for gestational age was 19 per cent in this group, significantly greater than that of the normal group that by definition is 10 per cent ($\chi^2 = 13.88$; $P < 0.001$). Despite this, in comparing the length of these newborns with the normal population's patterns, no differences were observed (5).

Final Comments

It is important to consider that in this kind of classification, as well as in others that have been proposed, the categories are not mutually exclusive and there are many ambiguous cases. However, when programs to reduce the incidence of low birth weight in a given population are planned, the knowledge of the predominant type of IUGR, if such exists in that population, could help in the selection process for interventions. In this way, a severely malnourished population with nonexistent or poor prenatal control, and a significant percentage of Type I (proportionate IUGR), cannot be expected to

respond adequately to supplementation programs implemented in the third trimester of pregnancy. Such programs would have little impact. On the other hand, this kind of program would work successfully in populations with moderate protein-calorie malnutrition where nutrient deficiencies appear during the second and third trimesters.

This could have been the case in the Guatemalan longitudinal study where significant improvement in fetal weight occurred following nutritional intervention in women with moderate protein-calorie malnutrition (11). Likewise, it is possible that the same forces were at play in the Bogota study, where it was found that supplementation did not affect either birth weight or incidence of low birth weight when the whole sample was studied (18). Nevertheless, when the mothers were divided according to initial intake, those with better diets before pregnancy were found to have improved fetal weights after supplementation (19). This fact suggests that supplementation in the third trimester has an effect only on moderately malnourished mothers.

Finally, despite the above, a real and permanent reduction in the number of infants suffering from all three types of IUGR can be achieved only if, concomitant with public health interventions, the socioeconomic standards of the populations are improved.

Acknowledgment—We express our gratitude to Prof. J. M. Tanner for the critical review of this manuscript.

REFERENCES

1. Belizan, J. M., Lechtig, A., and Villar, J.: Distribution of low birth weight babies in developing countries. Am. J. Obstet. Gynecol. 132: 704, 1978.
2. Belizan, J. M., Nardin, J. C., Villar, J., Nardin, C. A., Malamud, J., Vicuma, L. S., Tenzer, S. M., and Nieto, F.: La altura uterina, el perimetro abdominal y el incremento de peso materno como indicadores del crecimiento intrauterino. In *Aspecto Perinatales del Parto Prematuro*, edited by O. Althabe and R Schwarcz. Editorial El Ateneo, Buenos Aires, Argentina, 1978, pp. 41–50.
3. Belizan, J. M., Villar, J., Nardin, J. C., Malamud, J , and Vicuna, L. S.: Diagnosis of intrauterine growth retardation by a simple clinical method: measurement of uterine height. Am. J. Obstet. Gynecol. 131: 543, 1978.
4. Campbell, S.: Assessment of fetal development by ultrasound. Clin. Perinatol. 1: 507, 1974.
5. Curbelo, V.: *Crecimiento Fetal Intrauterino*. Centro Latinoamericano de Perinatologia, Montevideo, Uruguay (Publicacion Cientifica No. 648), 1977, pp. 20–26.
6. Davies, D. P., Gray, O. P., Ellwood, P. C., and Abernethy, M.: Cigarette smoking in pregnancy: Associations with maternal weight gain and fetal growth. Lancet 1: 385, 1976.
7. Edwards, L., Alton, I., Barrada, M., and Hakanson, E.: Pregnancy in the Underweight Woman. Am J Obstet Gynecol 135: 297, 1979
8. Gruenwald, P.: Intrauterine growth. In *Perinatal Physiology*, edited by U. Stave. Plenum, New York, 1978, pp 1–18.
9. Guayasamin, O , Benedetti, W., and Althabe, O . Crecimiento Fetal Human Valorado por Indicadores Antropometrices. Boletin de la Oficina Sanitaria Panamericana. 31: 481, 1976.
10. Kurjak, A., Latin, V., and Polak, J.: Ultrasonic recognition of two types of growth retardation by measurement of four fetal dimensions. J. Perinat. Med. 6: 102, 1978.
11. Lechtig, A., Habicht, J. P., Delgado, H., Klein, R. E., Yarbrough, C., and Martorell, R.: Effect of food supplementation during pregnancy on birth weight. Pediatrics 56: 508, 1975.
12. Lechtig, A., Margen, S., Farrell, T., Delgado, H., Yarbrough, C., Martorell, R., and Klein, R. E.: Low birth weight babies: world-wide incidence, economic cost and program needs. In *Perinatal Care in Developing Countries*, edited by G. Rooth and L. Engstrom. University of Uppsala, Uppsala, 1977, pp. 17–30.
13. Lovell, K. E.: The effect of postmaturity on the developing child. Med. J. Australia 1: 13, 1973.
14. Lubchenco, L., Hausman, C. H., and Boyd, E.: Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. Pediatrics 37: 403, 1966.
15. Mata, L.: *The Children of Santa Maria Cauque: A Prospective Field Study of Health and Growth*. MIT Press, Cambridge, Massachusetts, 1978.
16. Miller, H. C., and Hassanein, K.: Fetal malnutrition in white newborn infants: Maternal factors. Pediatrics 52: 504, 1973.
17. Miller, H., Hassanein, K., and Hensleigh, P.: Fetal growth retardation in relation to maternal smoking and weight gain in pregnancy. Obstet. Gynecol. 125: 55, 1976.
18. Mora, J. O., Paredes, B., Wagner, M., et al.: Nutritional supplementation and the outcome of pregnancy. I. Birth weight. Am. J. Clin. Nutr. 32: 455, 1978.
19. Mora, J. O.: Personal communication, 1979.
20. Persson, P. H., Grennert, L., and Gennser, G.: Diagnosis of Intrauterine Growth Retardation by Serial Ultrasonic Cephalometry. Acta Obstet. Gynecol. Scand. Suppl. 78: 40, 1978.
21. Rohrer, F.: Der Index der Korperpirtle als Mass des Ernahrungszustandes. Munch. Med. Wochenschr. 68: 580, 1921.
22. Rosso, P., and Winick, M.: Intrauterine growth retardation: a new systematic approach based on the clinical and biochemical characteristics of this condition. J. Perinat. Med. 2: 147, 1974.
23. Streeter, G. L.: Weight, sitting height, head size, foot length and menstrual age of the human embryo. Contrib. Embryol. 11: 143, 1920.
24. Tanner, J. M.: *Fetus into Man*. Harvard University Press, Boston, Massachusetts, 1978, pp. 40–42.
25. United States Public Health Service: *Smoking and Health*. A Report of the Surgeon General. Pregnancy and Infant Health. Washington, D. C., U. S. Government Printing Office Publication, 79-50069, 1979, pp. 8.3–8.93.
26. Urrusti, J., Yoshida, P., Velasco, L., et al.: Human fetal growth retardation: I. Clinical features of sample with intrauterine growth retardation. Pediatrics 50: 547, 1972.
27. Widdowson, E. M.: Growth and composition of the fetus and newborn. In *Biology of Gestation*, edited by N. S. Assali. Academic Press, New York, 1968, pp. 40–42.