Epidemiology

Professor E.D. Alberman

INTRODUCTION

The first stage of any epidemiological study is to reach an agreement on the definition of the condition being reviewed. The term fetal undergrowth implies undergrowth for a given gestational age, and the first problem is that of measurement of gestational age. Even if this can be established, it is not obvious that norms of birthweight for gestational age for babies born pre- or post-term are representative of all conceptions that have reached that gestational age. They are likely to have characteristics associated with their gestational age at birth which may confound the epidemiology of any apparent undergrowth. These are points which will be discussed elsewhere in this volume.

However even if we consider only term births which constitute the majority of deliveries, variations of birthweight distribution between different socio-biological and population subgroups are such that it is problematical to arrive at an agreed "norm" from which to assess the associations and consequences of deviation. Stein and Susser[1] have pointed out the distinction, in this context, between the statistical "norm", which delimits the modal area of variation of a measure, and the "clinical norm", which distinguishes "all that is unimpaired, functioning and well from all that is impaired, malfunctioning and ill", and certainly this is a useful distinction to make. Unfortunately adverse consequences of undergrowth may not be perceived at birth, and again questions of definition of what is a malfunction or impairment would arise. In practice one is left with a definition which is largely statistically based, although many attempts have been made to render this more pragmatic. One cannot therefore escape some discussion of the statistical background of the definition of fetal undergrowth.

In addition it is becoming clear that fetal undergrowth takes many different forms, stunting and wasting being two such forms which are described. As yet the epidemiology of the different forms is not well worked out, and will not be further referred to in this paper.

THE DISTRIBUTION OF BIRTHWEIGHTS

There is general agreement that birthweight distributions, whether for all gestational ages or for a given gestational age, are of a shape that resemble, but are not strictly a Gaussian, or "normal" form. One particular departure from the normal is a tendency towards an excess in the tail of babies of low birthweight, which can

F. Sharp et al. (eds.), *Fetal Growth*

be reduced but not eliminated by restricting the curve to a specific gestational age. It is the births in these tails which represent, for a given gestational age, those babies who are undergrown, and there are two main ways of defining these statistically. One is to express them in terms of a given percentile of all birthweights for that gestational age, and cut-off points used have been the 3rd, 5th or 10th. The other is to express them in terms of the deviation from the mean, making the assumption that the distribution is basically Gaussian, and defining them as under two standard deviations from the mean, a measure which in a Gaussian distribution corresponds to just under the 3rd percentile. In practice, since the distributions can be shown to depart in several ways from the Gaussian form, the use of percentiles is probably the better choice.

BIOLOGICAL INFLUENCES ON THE DISTRIBUTION

There are certain biological influences on the distribution which are marked and consistent. These include sex, plurality, birth order, and maternal height, weight and birthweight. These are each of a different nature and it is worth considering them separately.

Sex and plurality

Fetal sex seems to have its own independent effect on fetal growth, birthweight of males being higher on average than that of females of the same gestational age. In effect it means that the "norms" for males and females differ and, as Stein and Susser[1] pointed out, the importance of this is illustrated by the fact that at a given weight for gestational age girls have an advantage over boys in terms of perinatal survival and neonatal course. A similar situation pertains in the case of multiple births but in this case the relative retardation of growth in multiple births is secondary to a cause extrinsic and not intrinsic to the fetus.

Birth order

Relative growth retardation is also seen in first births, although it may be mitigated if preceded by a spontaneous abortion.[2] In this case also it may be presumed that the cause is extrinsic to the fetus, but this time it seems that no fetal benefit is gained in relation to later births of the same birthweight and gestational age. It may be that the benefit is a negative one, in the sense that the dangers to large first babies may be greater than for other birth orders. However, Stein and Susser[1] argued that, in contrast to the situation with fetal sex and plurality, we should not use different norms for first and later births from which to assess fetal undergrowth.

Social and economic deprivation

Fetal growth rate is slowed under conditions of social and economic deprivation[3] whether this is measured using occupational, educational, or financial classifications. The mechanisms through which this slowing is mediated are certainly in part nutritionally based, both through maternal lifelong nutritional status, which may

permanently stunt growth, and through nutritional or general health status around the time of conception and pregnancy, reflected by maternal weight. These will be discussed in depth elsewhere in this volume, but they bear directly or indirectly on much of the epidemiology of fetal undergrowth in relation to other factors.

Adverse factors other than nutrition are also more common under conditions of deprivation: maternal infections, often the smoking habit, alcohol and drug abuse and occupational hazards, and close pregnancy spacing. The effects of these hazards will be discussed further later, but first one should consider the overall confounding effect of deprivation on apparently biological variables such as maternal height and ethnic group.

Parental height

Although both parents contribute towards the eventual height of their offpsring it is the maternal influence which is predominant in the case of birthweight. At least three mechanisms have been suggested through which this influence may reduce birthweight for gestational age. One is the purely genetic effect;[4,5] one is an immediate effect of severe maternal malnutrition which can be palliated with nutritional supplementation;[6] and finally there seems to be an effect which Ounsted and Ounsted[7] have termed "maternal constraint", which they have shown to be familial through the female line. Any or all of these are likely to be associated with

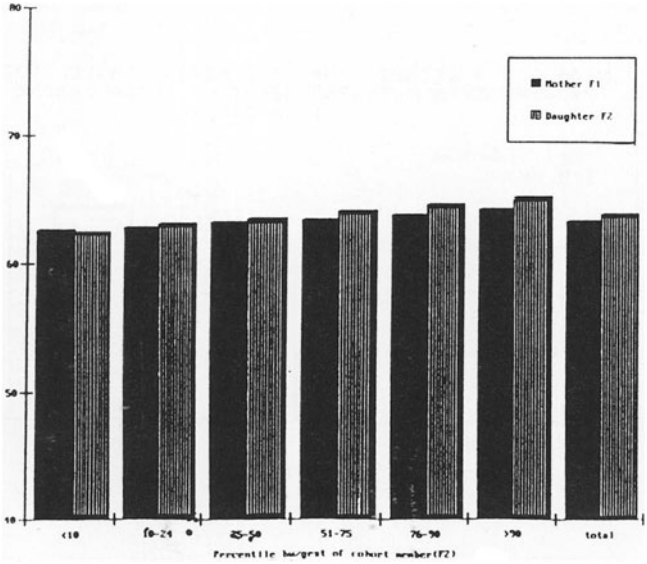

Figure I
Mean height in inches of female cohort member at 23 yrs and her mother by percentile bw/gest for cohort member – 1958 cohort
(Alberman *et al.* in preparation)

short maternal stature, and/or low maternal weight.

However there is potential circularity in these effects, since adult height in its turn is influenced by maternal birthweight. Figure I is taken from preliminary findings from an ongoing study of intergenerational effects in the 1958 National Birthday Trust Fund birth cohort[8] (Alberman *et al.* in preparation). Increasing birthweight for gestational age in the cohort members is associated on the one hand with an increase in the height of their mothers, and on the other with an increase in the height of cohort members at the age of 23 years. Interestingly, although the increases in height of the mothers and their adult daughters are closely associated, in those whose birthweight was less than the 10th percentile mean adult height was actually less than that of their mothers, while in all other groups it was greater.

Presumably this overall increase of height in the second generation is reflecting the steady secular increase in height that has been recorded in the developed countries. The exception in the case of the cohort members born small-for-dates may be reflecting maternal constraint, or a direct adverse effect of fetal undergrowth. These results are closely related with those of other studies relating birthweight in one generation to birthweight in the next.[9–11] This we are also able to look at in the 1958 cohort, and Figure II shows how the mean birthweight of the female children of the cohort members rises consistently as their mothers' birthweight for ges-

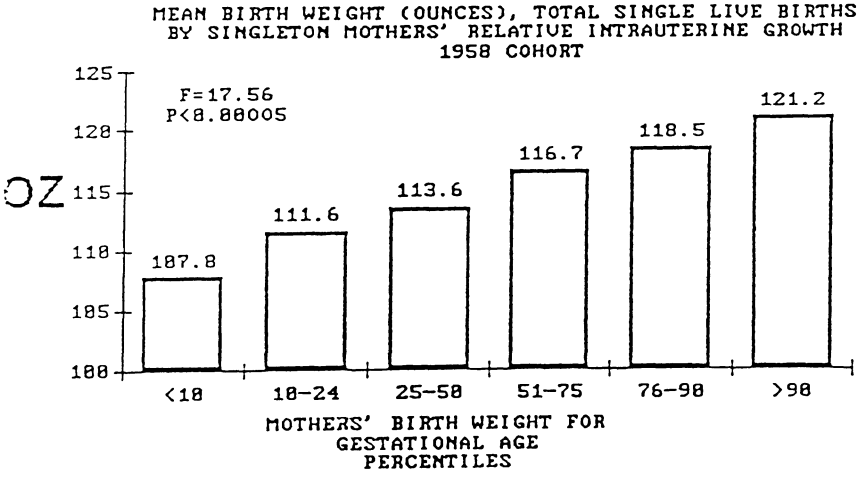

Figure II
Mean birthweight (ounces), total single live births by singleton mothers' relative intrauterine growth – 1958 cohort.
(Emanuel *et al.* in preparation)

tational age rises, and this was true also of the male children (Emanuel *et al.* in preparation). Unfortunately information on the gestational age of the children of the cohort is lacking, so we do not know which of those who were of low birthweight were growth retarded. It is hoped to collect this information at a later sweep. We do know from the literature that within sibships there tend to be recurrences of preterm births, and fetal growth retardation.

Important also in this respect is the evidence from Norway showing the tendency within sibships to repeat fetal growth retardation, and preterm birth.[12]

Ethnic group

As with maternal height, genetic factors must play some part in effecting the well known differences in birthweight distribution between ethnic groups.[7] However, as with maternal height, the situation is confounded by the close inter-relationships between ethnic group and social class, for until recently socio-economic advantage has been largely confined to white populations. This needs to be taken into account when comparing fetal growth rates in different populations.

Table 1. Percentage low birthweight and infant mortality rates in different ethnic groups

Singapore: 1967–74 Single live births % < 2500 g			
Gestational group	Chinese %	Malay %	Indian %
Pre term	32.4	28.1	40.4
Term	5.0	6.5	9.8
Post term	4.6	8.4	6.7
All	6.1	8.1	11.5
ENMR	11.6	14.3	12.1
NMR	13.8	17.6	14.7
PNMR	4.8	12.3	7.8

(Hughes *et al.*, reference 14).
ENMR = early neonatal mortality rate
NMR = neonatal mortality rate
PNMR = perinatal mortality rate

However there are some clear-cut comparisons; for instance the consistently high rate of low birthweight births in US blacks compared with US whites has long been recognised, and there are annual vital statistical reports showing that among blacks birthweight for gestational age is consistently lower than among whites.[13] Hoffman and his colleagues[13] and many others, have shown that they have a mortality advantage over white babies at low gestational ages. However the socio-economic status of the blacks in the US overall is markedly lower than that of the white population and the raised mortality rates of the black babies overall at term testifies to the effect of that disadvantage.

However there is data from Singapore[14] where, it is maintained, three ethnic groups, Chinese, Malay and Indian, live in the same social environment with total health care coverage. Table 1 shows the proportion of low birthweight live births born preterm, at term, and post-term in each of these ethnic groups, showing a marked excess of small-for-date births ($\leq$ 2500 g at term) in the Indian group. However the overall mortality rates, early neonatal, neonatal and perinatal are persistently highest in the Malay group, and intermediate in the Indians, in spite of their apparently disadvantageous weight distribution, 10% of their term births weighing 2500 g or less. It should be noted that overall the mortality rates, which were the average of those occurring between 1967–74, are relatively favourable compared with other countries for those years.

It seems that these weight differences may truly reflect genetic, or possibly intergenerational differences. However it would have been interesting to know the birthweight/gestational specific mortality rates, and also something of the adult heights in the different generations.

In general, as in the case of maternal height, it is important to be able to distinguish between apparently genetically determined relatively slow fetal growth in certain ethnic groups, and that determined by environmental disadvantage, for this raises the question of the choice of appropriate "norms" for different ethnic groups, and the selection of outcome measures to assess their appropriateness. A large number of different statistical strategies have been proposed to try to produce international norms which take into account ethnic environmental differences. This is discussed in some detail in a series of review papers edited by Wharton and Dunn[15] but it is fair to say that no simple solution has yet been proposed.

There are of course also very interesting questions as to the long term benefit or otherwise of striving to equalise birthweight distributions in different populations. In addition, little is known about the natural history of secular anthropometric changes, whether these start with increases in birthweight, or with increases in parental height. Certainly a change in a rate of fetal growth must be a part of this process.

Abnormal genetic effects

As well as the apparently subtle genetic effects which have been described there are some more clear-cut causes of fetal undergrowth.[4] Certain chromosomal anomalies, the most important of which is Down Syndrome, are known to cause fetal growth retardation, and there are also some single gene defects which cause

dwarfing. There have been interesting comments as to the relationship of some fetal malformations to generalised or localised growth retardation.[1] Certainly these are related, but whether causally or not, and, if not, which preceded the other is an important question. Thus congenital heart defects may be due to a slowing of certain development pathways.

Fetal or placental infection

It is well known that fetal infections lead to growth retardation, babies with rubella embryopathy, or cytomegalo virus infection commonly being small-for-dates. Worldwide, possibly the most important infective cause of low birthweight is malaria, which seems to act largely through infestation of the placenta.[16] There are probably very large numbers of other infections that contribute directly or indirectly to fetal growth retardation.

Maternal smoking and alcohol consumption

In the developed countries much of the fetal growth retardation that we see is attributable to maternal smoking, which can retard fetal growth to the extent that at term the babies of mothers who smoke may be on average 100–170 g lighter than those who do not.[17] Moreover the literature[18] on the effects of alcohol consumption in pregnancy is also pointing to the importance of drinking as an agent of fetal growth retardation (Table 2), with odds ratios of being small-for-dates rising consistently with the number of drinks consumed.

Table 2. Odds ratio for a small-for-gestational age birth by alcohol consumption adjusted by multiple logistic regression.

No. of drinks per day	Odds Ratio	95% confidence intervals
≤ 1	1.11	1.00 – 1.23
1 – 2	1.62	1.26 – 2.09
3 – 5	1.96	1.16 – 3.31
≥ 6	2.28	0.91 – 5.77

(Mills *et al.*, reference 18).

Occupational hazards

There is an increasing body of literature on the effect of work in pregnancy in relation to fetal growth. Many data sets have looked at birthweight alone, but a recent paper looking at pregnancy amongst obstetricians[19] has shown an excess of births of a weight under the 10th percentile for a given gestational age (standard used not

given). According to this, primiparous obstetricians delivering during their residency were significantly more likely to produce growth retarded babies compared with 8.2% in those born before and 1.0% born after, but this is a highly selected sample.

Altitude

Another circumstance under which fetal growth rate is retarded is pregnancy at high altitudes. It can be shown that birthweight distribution shifts in a systematic way to lower levels as altitude rises.[20] This effect has been compared by Meyer[21] to that of smoking, for under both circumstances relative placental weight is not reduced and similar structural changes occur, predisposing to antepartum haemorrhage.

Spacing of pregnancies

It has been shown that babies born after a short interval from a previous birth are likely to be of low birthweight.[22] Certainly in one population we have recently studied this seems to be due to fetal undergrowth rather than preterm birth. In births between 1978 and 1984, all of 37 weeks or later, to Bangladeshi mothers living in Tower Hamlets, birthweight is closely associated with length of the interval between the date of one birth and the next. Except at extremely long intervals it rises steadily as interval lengthens (Hilder, in preparation). This group of mothers is exceptional in the close spacing between pregnancies, but the picture seems to be consistent with the literature.

CONCLUSION

An attempt has been made to review some of the most important aspects of the epidemiology of fetal undergrowth, with the exception of the effects of pregnancy pathology, of which hypertensive disease is probably the most important, and which would warrant a chapter on its own. The whole subject is enormously complex, but its study is exciting and rewarding. It provides many clues to the genetic and environmental patterns of fetal and adult growth, as well as being associated with numerous different pathological conditions. We have much to learn yet, and a necessary prerequisite for a fuller understanding is better data on a population scale of reliable gestational age as well as birthweight data.

ACKNOWLEDGEMENTS

Preliminary reports have been included from a study of intergenerational effects on reproduction funded by the National Institutes of Health and the Thrasher Research Fund.

REFERENCES

1. Stein ZA, Susser M. Intrauterine growth retardation: epidemiological issues and public health significance. *Semin Perinatol* 1984; **8**: 5-14.
2. Alberman E, Roman E, Pharoah POD, Chamberlain G. Birthweight before and after a spontaneous abortion. *Br J Obstet Gynaecol* 1980; **87**: 275-280.
3. Baird D. Epidemiologic patterns over time. In: *The Epidemiology of Prematurity.* Eds: DM Reed, FJ Stanley. Graz: Urban and Schwarzenberg 1977: pp.5-15.
4. Polani PE. Chromosomal and other genetic influences on birth weight variation. In: *Size at Birth.* Eds: K Elliott, J Knight. Ciba Foundation Symposium 27. Amsterdam: Elsevier. 1974: pp.127-164.
5. Morton NE. Genetic aspects of prematurity. In: *The Epidemiology of Prematurity.* Eds: DM Reed, FJ Stanley. Urban and Schwarzenberg, 1977: pp.213-230.
6. Rush D, Alvir JM, Garbowski GC *et al.* The National WIC Evaluation; evaluation of the special supplemental food programme for women, infants and children. *Am J Clin Nutr* 1988; **48**:
7. Ounsted M, Ounsted C. *On Fetal Growth Rate.* Clinics in Developmental Medicine, No 46. London: Spastics International Medical Publications, 1973.
8. Butler NR, Bonham DG. *Perinatal Mortality.* Edinburgh: E and S Livingstone, 1969.
9. Klebanoff MA, Graubard BI, Kessel SS, Berendes HW. Low birth weight across generations. *JAMA* 1984; **252**: 2423-2427.
10. Hackman E, Emanuel I, van Belle G, Daling J. Maternal birth weight and subsequent pregnancy outcome. *JAMA* 1983; **250**: 2016-2019.
11. Carr-Hill R, Campbell DM, Hall DM, Meredith A. Is birth weight determined genetically? *Br Med J* 1987; **295**: 687-689.
12. Hoffman HJ, Bakketeig LS. Heterogeneity of intrauterine growth retardation and recurrence risks. *Semin Perinatol,* 1984; **8**:15-24.
13. Hoffman HJ, Stark CR, Lundin FE, Ashbrook JD. Analysis of birth weight, gestational age, and fetal viability. *Obstet Gynecol Surv* 1974; **29**: 651-681.
14. Hughes K, Tan NR, Lun KC. Low birthweight of live singletons in Singapore. *Int J Epidemiol* 1984; **13**: 465-471.
15. Wharton B, Dunn PM. Perinatal growth: The quest for an international standard for reference. *Acta Pediatr Scand* Supplement 319, 1985.
16. McGregor IA, Wilson E, Billewicz WZ. Malaria infection of the placenta in The Gambia, West Africa; its incidence and relationship to stillbirth, birthweight and placental weight. *Trans R Soc Trop Med Hyg* 1983; **77**: 223-244.
17. Butler NR, Alberman ED. *Perinatal Problems.* Edinburgh: E and S Livingstone, 1969.
18. Mills JL, Graubard BI, Harley EE, Rhoads GG, Berendes HW. Maternal alcohol consumption and birth weight. How much drinking during pregnancy is safe? *JAMA*; **252:**1875-1879.
19. Grunebaum A, Minkoff H, Blake D. Pregnancy among obstetricians: a comparison of births before, during and after residency. *Am J Obstet Gynecol,* 1965; **15**:329-352.

20. Grahn D, Kratchman J. Variation in neonatal death rate and birth weight in the US and possible relations to environmental radiation, geology and altitude. *Am J Hum Genet* 1965; **15:** 329–352.
21. Meyer MB. Effects of maternal smoking and altitude on birth weight and gestation. In: *The Epidemiology of Prematurity.* Eds: DW Reed, FJ Stanley. Baltimore, Munich: Urban and Schwarzenberg, 1977: pp.81-104.
22. Federick J, Adelstein P. Influence of pregnancy space on outcome of pregnancy. *Br Med J* 1973; **4**:753-756.