

REPRINTS AND REFLECTIONS

Transmission through the female line of a mechanism constraining human fetal growth[†]

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Cross-breeding experiments between large and small strains of mammals have shown the powerful influence of the maternal organism on the control of fetal growth. The prepotency of a maternal regulator has also been demonstrated in humans. Our earlier studies indicated that this regulator acts by means of constraint; there is no equivalent accelerating mechanism. Data on 1092 siblings and 5207 paternal and maternal relatives of 986 probands show different patterns of birthweight among families ascertained, respectively, through very large and very small babies. When constraint is relaxed the Mendelian laws of inheritance are clearly followed. At the lower extreme there is evidence for the transmission of constraint through the female line only. This could be due to the maternal genotype, but our data suggest that a non-Mendelian path might also be involved. Such a process would be adaptive, facilitating fairly fast changes in fetal growth rate as the conditions under which a population lives deteriorate or improve.

1. Introduction

Classic cross-breeding experiments between Shire horses and Shetland ponies first demonstrated the potency of the maternal regulation of fetal growth.¹ In cattle the constraint exerted by the small Dexter dam was much greater than the enhancement allowed by the large Devon.² Similar experiments with rabbits showed that the maternal influence was transmitted to the F2 generation.³ In human families there is a high correlation in birthweight ($r=0.581$) between maternal half siblings, but only a low one ($r=0.102$) between paternal half siblings.⁴ The variance in birthweight of the offspring of monozygous twins is four times greater through males than females.⁵ Thus in our own species also, the prepotency of the maternal influence is manifest.

Robson⁶ found that the correlation between birthweights of maternal first cousins was positive, whereas the correlation in birthweight between

paternal and mixed first cousins did not depart significantly from zero. Re-analysing the same data, Penrose (personal communication) found that when the probands were of low birth weight, first cousins through maternal aunts were lighter than other types of first cousin. Our own earlier analyses of the birthweights of maternal relatives of small-for-dates (SFD) and large-for-dates (LFD) babies led to the following theoretical propositions:^{7,8}

1. In mammals, maternal systems constrain fetal growth rate to match that of the maternal strain.
2. Maternal constraint is prepotent at the lower extreme; at the upper extreme relaxation of constraint allows other factors to take up more of the variance.
3. The set-point of the constraining mechanism is adjusted *in utero* in female fetuses.

During the intervening years we have enlarged and extended our data base. In addition to data from the maternal side, information was obtained on the birthweights of SFD and LFD relatives on the paternal side. A third group of pedigree data associated with infants who were average-for-dates (AFD) at birth has also been included. It is now possible directly to investigate the paternal influence on birthweight, and

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to compare the pedigree patterns and the birthweights of different classes of relative in the two extreme groups with those obtained through probands whose fetal growth rate was within the normal range. The transmission of the maternal influence is thereby set in a broader perspective.

2. Materials and methods

The probands were all born in Oxford between 1964 and 1975. They were participating in a study of the factors associated with SFD and LFD pregnancies.⁹ Thus infants at the two extremes of the birthweight distribution were specifically sought. The criteria were that they should be more than 2SD below or above the mean, respectively, for gestational age and sex.¹⁰ Women in the adjacent beds bearing AFD babies, whose birthweights were all within 2SD of the mean according to the same standards, were invited to join the study as a comparison group. All were singleton Caucasian births. The mothers were personally interviewed after delivery and their babies examined by medical members of a small research team. With the mother's help a family tree containing all the baby's relatives was drawn up, each member being personally named. These were then transferred to a standard form which was taken away and filled in with the aid of the baby's maternal and paternal aunts and grandmothers. On return the forms were carefully scrutinized. Some were incomplete owing to the death, separation or emigration of the appropriate female source of information. Birthweights that were clearly recorded in pounds and ounces were accepted; but apparently inaccurate data, for example, 'about 7½lbs', were excluded. All values were thereafter transposed to grams, and submitted to computer

analysis. Information is presented on the birthweights of 1092 siblings and 5207 paternal and maternal relatives of 986 probands. *F* tests have been used to analyse the data where appropriate.

3. Results

Some basic information about the probands is given in table 1. By criterion mean birthweights in the two extreme groups diverged: their range was relatively small and distributions skewed. Differences in mean gestational age were small, and mainly due to differences in the number of pre-term babies in the three groups (SFD 6.1%, AFD 3.1%, LFD 0.5%).

The mean birthweights for each class of relative in the three groups are arrayed in table 2. For single-sex relatives adjustment has been made by adding (to female) or subtracting (from male) 70 g of the mean value. In each group the mean birthweight of previous live-born siblings approximates that of the probands. There is a highly significant difference

Table 1 Information about probands

| | Birthweight group | | |
|-------------------------------|-------------------|-------------|-------------|
| | SFD (N=428) | AFD (N=193) | LFD (N=365) |
| <i>Birthweight (g)</i> | | | |
| Mean | 2.164 | 3.347 | 4.570 |
| SD | 0.290 | 0.408 | 0.244 |
| Range | 0.910–2.610 | 2.260–4.430 | 4.110–5.700 |
| <i>Gestational age (days)</i> | | | |
| Mean | 276.4 | 277.6 | 280.0 |
| SD | 10.6 | 9.8 | 8.7 |
| Range | 232–303 | 233–294 | 247–300 |

Table 2 Mean birthweights of different classes of relative ascertained through SFD, AFD and LFD babies

| | SFD (N=428) | | | AFD (N=193) | | | LFD (N=365) | | |
|-------------------|-------------|-----|-------|-------------|-----|-------|-------------|-----|-------|
| | Mean | SD | (N) | Mean | SD | (N) | Mean | SD | (N) |
| Liveborn siblings | 2734*** | 596 | (352) | 3274 | 485 | (150) | 3963*** | 532 | (590) |
| <i>Maternal</i> | | | | | | | | | |
| Mothers | 2973*** | 680 | (267) | 3337 | 586 | (124) | 3782*** | 583 | (258) |
| Mothers' sisters | 3214 | 698 | (231) | 3361 | 537 | (109) | 3606*** | 590 | (230) |
| Mothers' brothers | 3139*** | 634 | (193) | 3409 | 641 | (100) | 3636** | 642 | (257) |
| Aunts' children | 3091*** | 553 | (269) | 3308 | 474 | (109) | 3566*** | 591 | (260) |
| Uncles' children | 3257 | 506 | (126) | 3403 | 641 | (51) | 3469 | 526 | (241) |
| <i>Paternal</i> | | | | | | | | | |
| Fathers | 3186 | 754 | (196) | 3336 | 714 | (116) | 3636*** | 658 | (228) |
| Fathers' sisters | 3289 | 699 | (170) | 3251 | 562 | (102) | 3565*** | 650 | (174) |
| Fathers' brothers | 3349 | 614 | (157) | 3350 | 639 | (88) | 3575* | 751 | (208) |
| Aunts' children | 3242 | 629 | (195) | 3300 | 598 | (128) | 3444* | 545 | (192) |
| Uncles' children | 3101 | 579 | (137) | 3212 | 542 | (105) | 3418** | 594 | (186) |

P* < 0.05, *P* < 0.01, ****P* < 0.001, in each case represents differences from the same class of AFD relative.

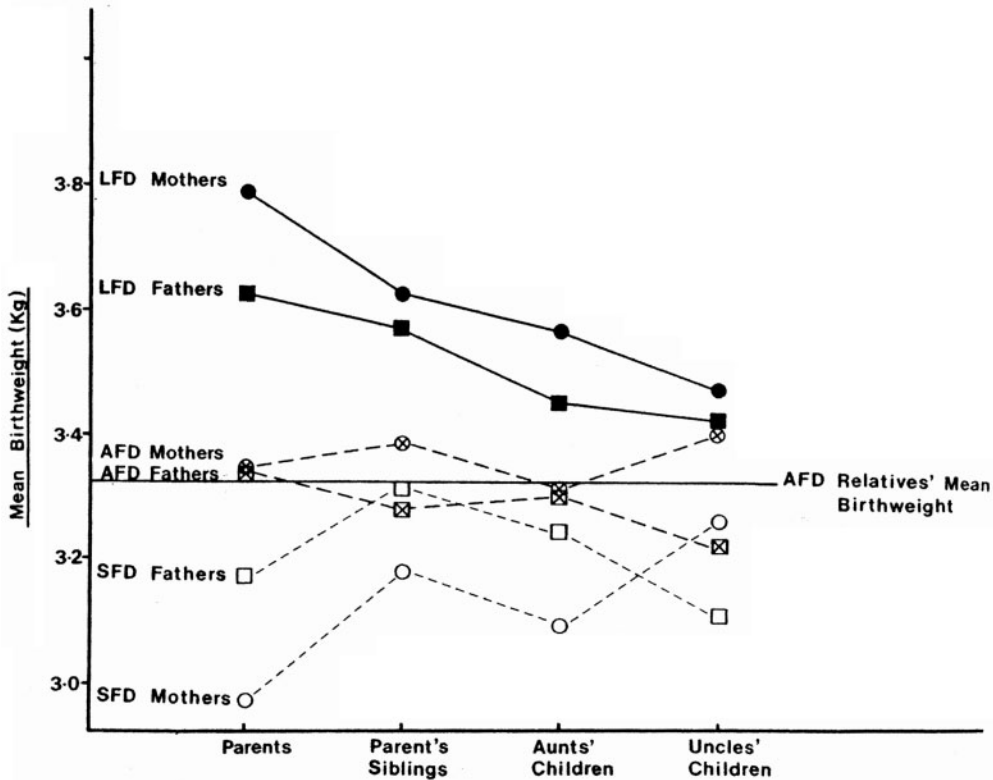


Figure 1 Mean birth weights of paternal and maternal relatives

between the birthweights of the mothers in the three groups. Within the two extreme groups maternal birthweights were significantly lower (SFD) and higher (LFD) than those of other maternal relatives ($P < 0.001$). LFD fathers were also marginally heavier than other LFD paternal relatives; but there were no differences between the birthweights of fathers and other paternal relatives in the SFD group.

In the AFD group the birthweights of all relatives clustered around the mean for the probands and the population from which they were drawn. The relatives of LFD probands were all above average in birthweight. On both maternal and paternal sides the values decrease with increasing genetic distance from the proband. In the SFD pedigrees no clear patterns emerge. The mean birthweights of paternal relatives do not differ from their counterparts in the AFD group. On the maternal side the values are generally lower. They range from first cousins through maternal aunts, who are nearest to mothers in the birthweight order, through maternal uncles and aunts to first cousins through maternal uncles, who are of average birthweight. First cousins through maternal aunts are lighter than first cousins through maternal uncles ($P < 0.02$), they are also lighter than their own mothers ($P < 0.05$).

Analyses of variance were done on the birthweights of four classes of relative within each group (figure 1, table 3), adjustments being made for sex, as before, where appropriate. Two variables were used

in the analyses: (1) type of relative (parent, aunt or uncle, aunt's child, uncle's child); (2) paternal or maternal 'side'. In the SFD group significant differences are found according to the side and the type of relative. The interaction data indicate that the pattern of birth weights on the paternal side differs from that on the maternal side to a highly significant degree. The LFD group also showed significant differences according to type of relative, and side, but in this group the pattern of birth weights on the two sides did not differ. There are no differences for any source of variation in the AFD group.

4. Discussion

Our criteria for entry to the two extreme groups were strict. Only women whose last menstrual period (LMP) was normal, accurately known, and not a withdrawal bleed from the pill, with a cycle not exceeding 32 days were included. We also excluded those women whose fundal height at first examination was not equivalent to their dates. Some women have unusually large babies at gestational ages below 37 weeks.^{11,12} This is thought to be due to bleeding episodes after the start of pregnancy being mistakenly recorded as the LMP. 'Correction' has been made for this in some birthweight-for-gestation charts,¹³ but not in the ones we used.¹⁰ The large SDs at these earlier gestation periods precluded the admission of

Table 3 Analyses of variance of relatives' birthweights (kg)

| Group and source of variation | SS | DF | MS | F |
|-------------------------------|--------|------|------|-----------|
| <i>SFD</i> | | | | |
| Side | 5.61 | 1 | 5.61 | 13.56*** |
| Type of relative | 9.77 | 3 | 3.26 | 7.88*** |
| Interaction | 6.74 | 3 | 2.25 | 5.43*** |
| Residual | 799.52 | 1934 | 0.41 | |
| Total | 821.76 | 1941 | 0.42 | |
| <i>AFD</i> | | | | |
| Side | 1.13 | 1 | 1.13 | 3.19 n.s. |
| Type of relative | 0.60 | 3 | 0.20 | 0.57 n.s. |
| Interaction | 0.96 | 3 | 0.32 | 0.91 n.s. |
| Residual | 362.23 | 1025 | 0.35 | |
| Total | 365.17 | 1032 | 0.35 | |
| <i>LFD</i> | | | | |
| Side | 4.07 | 1 | 4.07 | 10.93*** |
| Type of relative | 19.31 | 3 | 6.44 | 17.28*** |
| Interaction | 1.20 | 3 | 0.40 | 1.08 n.s. |
| Residual | 829.22 | 2226 | 0.37 | |
| Total | 853.38 | 2233 | 0.38 | |

*** $P < 0.001$, n.s., not significant.

some potential LFD probands to our studies, and accounts for the relative lack of pre-term babies in this group. The excess of SFD pre-term infants compared with the AFD group was due to higher obstetric intervention rates to expedite the early delivery of these 'at risk' fetuses. These minor differences will not have affected our findings, however, since although the correlation for birthweight among siblings is high, that for gestational age is low.¹⁴ Our data were all recorded shortly after the proband's birth: subsequent siblings have not, therefore, been included. It is, perhaps, noteworthy that there were many more previous live-born siblings per LFD proband than in the other two groups. This is because the relative risk of having an LFD baby steadily rises with increasing parity, whereas the chances of having an SFD baby are unaffected by parity.⁹

The level at which the maternal regulator is set is fairly constant in any given woman.⁸ The relative risk of having a very small or large baby is much enhanced if previous babies have been very small or large, respectively,^{15,16} and the risks remain high after account has been taken of other factors affecting fetal growth rate which may be present in succeeding pregnancies.¹⁷ This has important clinical implications. Intrauterine growth retardation is associated with many types of congenital abnormality.¹⁸ Thus when an SFD baby is born into a sibship of average birthweight, fetal abnormality should be strongly suspected. The evidence for fetal growth retardation

need only be relative. A child of average birthweight born into a LFD sibship is equally at risk. Likewise, if unusual clinical features are noted after birth, or his subsequent growth or development give rise to concern, the 'odd-man out' in the sibship, according to this rule, should be thoroughly screened to exclude abnormalities of congenital origin.

Two other studies have investigated the birthweights of some distaff relatives of low birthweight babies. In Aberdeen,¹⁸ where comprehensive records have been kept since 1948, the reproductive performance of sisters and sisters-in-law was examined. Sisters of women who had delivered SFD babies had lighter offspring than sisters-in-law, the general population, or sisters of women who had given birth to pre-term infants of low birthweight. Account was taken of gestational age, Fetal sex, and the height, weight, parity and smoking habits of the mothers. Their low birthweight could not, therefore, be due to similarities in the mothers' and maternal aunts' stature and lifestyle. In Hungary¹⁹ the birthweights of siblings, mothers, maternal aunts and their children were collected. Reliable information was available on the families of 1042 probands. There were four groups ascertained through full-term SFD, AFD, LFD and 'true premature' neonates. Mean birthweights of relatives in the true premature group were only a little lower than AFD probands and their relatives. In the other three groups a close correlation was found between the birthweights of the probands, their mothers and maternal relatives in every case. Mean values for relatives in the SFD group were all 2.75 kg or less; in the LFD group they were all 3.68 kg or more. The AFD group showed little variation in mean birthweights. These findings are consistent with the theory that the rate of fetal growth is influenced by a familial component with maternal transmission.

In our LFD group mean birthweights of relatives on the paternal side were almost as high as those on the maternal side, and their values decrease as their genetic likeness with the probands becomes smaller. The strong effect of biological factors on fetal growth rate at the upper extreme is apparent here. Assortive mating^{20,21} will have contributed to the high birthweights on the paternal side, but there is also some evidence for an association between paternal stature and birthweight, at the upper extreme, which is independent of maternal height.²² Analyses of these factors according to different social-class groupings led the authors to conclude: 'Tall paternal stature relates to a favourable environmental and genetic component among the factors influencing birthweight'.

In the SFD group the pattern of birth weights on the paternal and maternal sides differed from those in the LFD group, and from each other. On the paternal side the birthweights of each class of relative were similar to those in the AFD group. This supports the notion that the father plays a negligible role when maternal constraint is prepotent. The low mean birthweights of

mothers and first cousins through maternal aunts in this group points to the transmission of constraint through the maternal genome. This seems unlikely, however, to be the only process involved. The genetic affinity of first cousins is only half that of aunt and proband, but the birthweights of first cousins through maternal aunts converged closer on the SFD probands than did those of maternal aunts. Since the set of the constraining mechanism is fairly constant in any given woman, mothers and maternal aunts would have experienced a similar degree of constraint *in utero*. We propose that it is this, rather than their own response to it, that is transmitted, and affects in turn the fetal growth rate of their children.

Other maternal factors associated with SFD babies include low weight and height, smoking, hypertension and pre-eclampsia during pregnancy. Fetal infections and abnormalities also make a contribution. In order to test our hypotheses further, and to assess the interactions of these other factors with maternal constraint, we are now analysing our data in respect of all these parameters. If maternal constraint is mediated in part through maternal size, as in other mammals, we would expect the pedigrees of SFD children born to small women to show the typical pattern more than those born to large mothers. In the presence of heavy smoking severe pre-eclampsia or fetal abnormalities, the constraining pathway is unlikely to be manifest.

Ethnic variation in birthweight is large. Reported mean values range from 2.40 kg to 3.88 kg.²³ The differences between groups have no obvious explanation, and secular trends have been recorded in both directions.^{24,25} Studies of birth weights in Israel are illuminating. Infants born to immigrants from North African countries were heavier, and those from Asian countries lighter than the mean birthweight of second and third generation Israeli-born.²⁶ The maternal, but not the paternal, country of origin was the important factor influencing these findings.²⁷ Analyses of birth weights of second and subsequent generations of Israeli-born by origin of their grandparents showed a regression towards the mean, with those of African descent falling and those of Asian descent rising. This 'acculturation process' is of particular interest, since the African groups were predominantly of low socio-economic status, and a rising standard of living coincided with a falling birthweight.²⁸ Among more recent immigrants from Africa mean birthweights were inversely related to the number of years they had lived in Israel: those who arrived in their teens having heavier babies than those who came when they were younger, or had themselves been born there.

Although man has not speciated, human dispersal has been so wide that virtually all habitats have been occupied. The velocity of fetal growth is basic to the fitness (measured by reproductive achievement) of any population. Thus in equatorial countries where malnutrition has been rife for generations the birth of small but mature babies would be advantageous.

A compromise is thereby made between the mother and her offspring's separate demands for inclusive fitness.²⁹ But in every population studied, optimal birthweight (defined as that weight at which perinatal mortality is lowest) is higher than mean birthweight.³⁰ There is therefore a continuing evolutionary selection towards faster fetal growth rate. Subtle mechanisms are needed to facilitate changes in fetal growth rate as the conditions under which a population lives improve or deteriorate.

It is clear that a maternal regulator controls the growth rate of the mammalian fetus. Our data confirm earlier proposals that this acts by means of constraint; when it is relaxed other biological factors take up more of the variance. Transmission is effected through the female line, and may be attributable to the maternal genome. However, this does not wholly accord with our findings, nor could it account for the well-documented variations in fetal growth rate over historic time. A more flexible process than one due to simple selective pressures on the gene pool of a population is needed. A system whereby the maternal regulating mechanism took up part of its set from the intrauterine experience of the mother would allow for moderately fast secular trends in either direction, whilst preserving within any group the mean and range best suited to it.

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Commentary: On ‘Transmission through the female line of a mechanism constraining human fetal growth’—does it exist?

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In 1986, just before the start of the era of studies focusing on ‘fetal programming of adult disease’, Margaret Ounsted and colleagues¹ published a timely observational study, focusing on birth weight and fetal growth across generations.

Previously, results from animal studies, including the classical cross-breeding studies between large Shire horses and Shetland ponies, had strongly suggested

that the maternal effect on fetal growth overrides the paternal effect. Moreover, in another animal study, the maternal effect on fetal growth restriction was larger than the maternal effect on fetal growth enhancement.

Ounsted and colleagues used information on birth weight from relatives of infants (‘proband’) being born ‘small-for-gestational age’ (SGA; less than 2 standard deviations (SD) below the mean birth weight for gestational age), ‘large-for-gestational age’ (LGA; more than 2 SD above the mean) and ‘appropriate-for-gestational age’ (AGA; between –2 and +2 SD). In all relatives to LGA probands, birth weight was above the average. Mothers of LGA infants had (after