Factors influencing development of secondary ossification centres in the fetus and newborn

A postmortem radiological study

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Pryse-Davies, J., Smitham, J. H., and Napier, K. A. (1974). *Archives of Disease in Childhood*, 49, 425. **Factors influencing development of secondary ossification centres in the fetus and newborn: a postmortem radiological study.** Whole body radiographs of 379 consecutive perinatal necropsies were used to determine the presence and diameters of secondary ossification centres in the os calcis, talus, distal femur, proximal tibia, cuboid bone, and proximal humerus.

An estimate of the normal development for gestational age was obtained from 164 selected cases. The variation in number and size of bone centres was too wide for accurate estimation of maturity in the individual case, but ossification could be classified as relatively normal, advanced, or retarded, and comparisons made between groups of cases.

Retardation of ossification was found mainly in association with males and small-for-dates babies, but also in some congenital malformations such as the trisomy syndromes and some multiple births: retardation was suggested in association with toxæmia of pregnancy, increasing maternal age, and increasing parity.

Advanced ossification was mainly related to female babies but was also found in relation to other malformations, especially anencephalus, and was suggested in association with Negro infants.

The time of appearance of secondary ossification centres in the skeleton has been used to estimate the maturity of the fetus both within and without the uterus, though such times of development have been found to vary fairly widely (see reviews by Adair and Scammon, 1921; Christie, 1949; Dee, Parkin, and Simpson, 1966). Much of the information concerning factors affecting ossification centre development has been obtained by assessing a limited number of bones in selected groups of live newborn and older children. As an alternative, the present study was undertaken to examine the development of ossification in whole body radiographs from a consecutive series of perinatal necropsies. In this way various controlling factors might be compared within a single population using the whole skeleton for assessment. Such a necropsy series would also be expected to provide greater

evidence of pathological features affecting growth and bone formation.

Materials and methods

Over a 4-year period, whole body radiographs were taken of 379 necropsies consisting of 53 abortions, 192 stillbirths, 127 early neonatal deaths, and 7 late neonatal deaths occurring up to the 18th day. Gestational age, expressed to the nearest completed week, ranged from 21 to 42 weeks after the first day of the last menstrual period. In 71 cases there was uncertainty about menstrual dates and gestational age was estimated from necropsy findings and ultrasound cephalometry when this measurement was available. Moderate or marked maceration was present in 97 stillbirths and abortions, and an attempt was made to determine the gestation at the time of intrauterine death from clinical records, radiographical or ultrasound evidence.

Anteroposterior and lateral whole body radiographs were taken before each necropsy and the presence of ossification centres in the os calcis, talus, distal femur,

proximal tibia, cuboid bone, and proximal humerus of right and left limbs was noted. Distances were arranged to maintain body size when exposing the films, and measurements of the maximum diameter of each centre were made.

Results

Range of ossification centre development.

The ossification centres appeared to develop in the order os calcis, talus, distal femur, cuboid bone, and proximal humerus. There were 8 exceptions: a cuboid centre without a proximal tibial centre (4 cases), a centre in the proximal humerus without a proximal tibial or cuboid centre (2), and a centre in the proximal humerus without a cuboid centre (2). In 24 of the 379 cases unilateral small ossification centres were found in equal numbers on the right and left sides. Only 6 cases showed a difference in the maximum diameters of bilateral centres and this did not exceed 2 mm. Cuboid ossification was found in 28 cases and 2 or 3 centres were present in half of these. Only 2 cases, at 39 and 41 weeks' gestation, showed evidence of very small carpal bone centres and the latter also showed lateral cuneiform ossification.

In order to compare groups of cases it was necessary to estimate a range of normal development. This was attempted by relating three measurements to gestational age. (1) The number of sites in which ossification centres had developed. (2) The total diameters of all the centres. (3) The diameters of both os calcis centres. The os calcis was selected because here ossification developed earliest and was present in 362 of 379 necropsies.

Then, 164 cases which were thought to be least abnormal with regard to growth assessment were selected by excluding cases with uncertain menstrual dates, moderate or marked maceration, late neonatal deaths, multiple births, and lethal malformations. This selected group included 38 of 139 small-for-dates babies with birthweights between the 5th and 10th centiles. Further exclusions would have made the numbers too small: there were insufficient cases for separate tables for males and females. Table I shows the pattern of ossification according to gestational age in the 164 selected cases. The normal number of ossification centres for the gestational age was restricted arbitrarily to the stage or stages comprising at least 60% of the total for each 2-week group. This normal range of ossification centre sites, together with the total ossification diameters and bilateral os calcis diameters, is given in Table II.

There is a significant correlation between the gestational age of the selected cases and the number

TABLE I

Development of ossification centres according to gestation in 164 selected normal perinatal necropsies

Gestation (wk)	No. of cases	No. of ossification centres present* (%)					
		0	1	2	3	4	5
21-22	5	80	20	—	—	—	—
23-24	10	30	60	10	—	—	—
25-26	19	16	63	21	—	—	—
27-28	15	—	33	67	—	—	—
29-30	23	—	35	61	4	—	—
31-32	13	—	—	85	15	—	—
33-34	13	—	—	68	15	15	—
35-36	18	—	6	22	50	22	—
37-38	12	—	—	—	42	50	8
39-40	22	—	—	9	32	42	13
41-42	14	—	—	—	21	14	36
Total	164	6	20	33	17	15	4

*0 to 6 indicates the presence of one or both of the 6 paired ossification centres. 0, no centres; 1, os calcis (OC) only; 2, OC + talus (T) only; 3, OC + T + distal femoral epiphysis (DF) only; 4, OC + T + DF with proximal tibial epiphysis (PT) or cuboid bone (C); 5, OC + T + DF + PT with C or proximal humeral epiphysis; 6, all 6 centres.

of ossification centres ($r = +0.84$, $P < 0.001$), the total ossification centre diameters ($r = +0.89$, $P < 0.001$), and the os calcis diameters ($r = +0.91$, $P < 0.001$). These measurements were used to grade development in a simple quantitative way without further reference to gestation dividing the 379 cases into the following 3 groups.

Normal (245 cases). The number of centres was normal and the total and os calcis diameters were within 2 SD of the mean.

Advanced (59 cases). 39 cases were regarded as advanced because the number of centres was 1 greater than normal. 20 cases were regarded as *significantly advanced* because the number was 2 or more greater than normal, or the total or os calcis diameters were more than 2 SD greater than expected for gestational age. These 20 cases included 3 with very large diameters but a normal number of centres.

Retarded (75 cases). 49 cases were regarded as retarded because the number of centres was 1 less than normal. 26 cases were regarded as *significantly retarded* because the number was 2 or more less than normal, or the total or os calcis diameters were more than 2 SD less than the mean. These 26 cases included 5 with very small diameters but a normal number of centres.

Factors influencing development of secondary ossification centres in the fetus and newborn 427

TABLE II

Data used to estimate normal, advanced, or retarded development of ossification centres based on 164 selected normal perinatal necropsies

Gestation (wk)	No. of cases	Accepted normal no. of centres* (mean $\pm$ SD)	Total diameters: all centres (mm) (mean $\pm$ SD)	Os calcis diameters: both centres (mm) (mean $\pm$ SD)
21-22	5	0	0	0
23-24	10	1	3 $\pm$ 3	3 $\pm$ 3
25-26	19	1	6 $\pm$ 4	6 $\pm$ 3
27-28	15	2	13 $\pm$ 6	9 $\pm$ 3
29-30	23	2	16 $\pm$ 7	12 $\pm$ 3
31-32	13	2	22 $\pm$ 6	15 $\pm$ 3
33-34	13	2	30 $\pm$ 11	17 $\pm$ 3
35-36	18	2 or 3	35 $\pm$ 10	20 $\pm$ 3
37-38	12	3 or 4	50 $\pm$ 12	22 $\pm$ 3
39-40	22	3 or 4	57 $\pm$ 12	24 $\pm$ 3
41-42	14	5 or 6	70 $\pm$ 16	26 $\pm$ 3
Total	164	—	—	—

*See footnote to Table I.

Features related to ossification centre development.

Male and female. There is a highly significant difference in relative ossification between the two sexes, seen in Table III (i), with the females showing

more advanced and the males more retarded development of ossification centres. The accelerated development in the female may also be shown by an analysis of the average deviation from the normal number of centres in the selected group

TABLE III

Features related to ossification centre development

Groups (total no.)	Ossification centre development (%)			P
	Normal	Advanced	Retarded	
(i) Male (214)	66	10 (3)	24 (8)	<0.001
Female (165)	64	22 (8)	14 (5)	
(ii) Small-for-dates: less than 10th centile birthweight (124)	58	12 (5)	30 (14)	<0.001
Normal-for-dates: 10-90th centile birthweight (198)	73	15 (4)	12 (2)	
(iii) Multiple births (24)	42	21 (0)	37 (17)	<0.05
Singletons (355)	66	15 (6)	18 (6)	
(iv) Congenital malformations (57)	46	24 (11)	30 (18)	<0.05
No congenital malformations (322)	68	14 (4)	18 (5)	
(v) European (324)	64	15 (5)	21 (7)	>0.05
Non-European (55)	67	20 (7)	13 (7)	
(vi) Negro (32)	66	25 (9)	9 (3)	Too few cases
Indian (18)	61	17 (6)	22 (17)	
Other non-European (5)	100	0 (0)	0 (0)	
(vii) Toxaemia of pregnancy and/or essential hypertension (31)	68	6 (3)	26 (6)	
No toxaemia nor hypertension (348)	64	17 (5)	19 (7)	>0.05
(viii) Primiparae (122)	64	20 (7)	16 (5)	
Multiparae (257)	65	13 (4)	22 (8)	>0.05
(ix) Maternal age (yr)				
16-24 (123)	68	16 (7)	16 (5)	
25-34 (197)	64	15 (5)	21 (6)	
35-46 (59)	59	17 (3)	24 (15)	
All cases (379)	65	15 (5)	20 (7)	

*Significantly advanced or retarded shown in parentheses.

of cases (Table I): the 68 females average 0.13 centres more than normal while the 96 males average 0.13 centres less than normal.

Small-for-dates babies. In the comparison of small-for-dates and normal-for-dates babies in Table III (ii), multiple births, late neonatal deaths, babies greater than the 90th centile birthweight for gestation, and babies less than 24 weeks' gestation have been excluded. The 10th centile birthweight limits used are those given by Thomson, Billewicz, and Hytten (1968) for 32 to 42 weeks' and those given by Lubchenco *et al.* (1963) for 24 to 31 weeks' gestation. The large percentage of babies with retarded ossification in the small-for-dates group is highly significant statistically and there is also a relative increase of significant retardation.

Multiple births. Table III (iii) shows that though the number of multiple births included in this series is small (24 babies), there is an increase in the percentage both of retarded and advanced ossification centre development when compared with singletons, and that these differences are significant. 5 pairs are included in this series: 4 pairs of twins and 2 triplets all dying within 11 hours of birth. The stage of ossification was the same for each of the pairs, though there was a diameter variation up to 3 mm in 3 pairs.

Congenital malformations. Table III (iv) shows a significant increase both of advanced and retarded ossification in babies with lethal malformations. The main types of malformation are indicated in Table IV showing correlations with ossification, sex, and growth retardation. A striking feature is the incidence of advanced ossification found in the 20 cases of anencephaly: only 1 case was judged

retarded. These anencephalic fetuses showed the usual high proportion of females and were mostly small-for-dates. A comparison of the advanced and normal anencephalic cases did not show any significant differences in the incidence of other malformations nor in the extent of spina bifida, adrenal hypoplasia, thymic hyperplasia, thyroid development, placental size, low birthweight, or maturity. Anterior pituitary tissue was confirmed histologically in 4 advanced and 4 normal cases. When the 20 anencephalic fetuses were compared with the 37 other malformations and with the 164 selected normal cases, the advanced ossification was significantly different ($P < 0.025$ and $P < 0.01$, respectively).

The 11 other CNS malformations included 8 with congenital hydrocephalus, 1 with cranium bifidum, and 2 babies with both prosencephaly and cebocephaly. In this subgroup there was an increase of small-for-dates babies and retarded ossification.

The 7 congenital heart lesions consisted of left-sided hypoplasia (3), persistent truncus arteriosus, transposition of great vessels, atrial and ventricular septal defects, and microcardia: a baby with left heart hypoplasia and another with septal defects were found to have Down's syndrome (proven trisomy 21). Only 2 showed retarded centre development, 1 of whom was a baby with Down's syndrome.

Of the 6 genitourinary tract malformations, 4 suffered renal dysplasia and showed Potter's syndrome: all 4 were small-for-dates, only 1 showed retarded ossification.

Four of the cases were diagnosed as trisomy D (13-15) and 2 as trisomy E (16-18): lymphocyte culture confirmed the karyotype in 5 babies, and 1 case of trisomy E was a pathological diagnosis.

TABLE IV

Relative development of ossification centres and incidence of associated features according to type of congenital malformation

Groups (total no.)	Ossification centre development (%)			Associated features (%)		
	Normal	Advanced	Retarded	Male	Female	Small-for-dates
Anencephaly (20)	55	40 (20)	5 (0)	15	85	90
Other CNS malformations (11)	55	9 (9)	36 (9)	36	64	82
Congenital heart disease (7)	43	28 (14)	29 (14)	71	29	14
Genitourinary malformations (6)	67	0 (0)	33 (17)	83	17	67
Trisomy D and E (6)	17	17 (0)	66 (66)	50	50	83
Other multiple malformations (5)	20	40 (0)	40 (20)	40	60	100
Thanatophoric dwarfism (2)	0	0 (0)	100 (100)	50	50	50
All congenital malformations (57)	46	24 (11)	30 (18)	40	60	75

'Significantly' advanced or retarded shown in parentheses.

Ossification in 4 of these cases (2 trisomy E and 2 trisomy D) was significantly retarded.

The other malformations included 4 babies with multiple abnormalities of unclassified type not involving the CNS and one acardiac acephalic twin. The twin and 1 of the multiple abnormalities showed some advance in ossification centre development, while 2 other cases showed some retardation.

There were also 2 cases of thanatophoric dwarfism, both showing significant retardation of ossification: 1 showed a reduced number of centres and both showed abnormally small centres.

Race. Table III (v) shows a greater percentage of advanced ossification in non-European babies and retarded ossification in European babies, but the differences do not reach statistical significance. Of 55 non-European babies, 32 were Negro, 18 were Indian, and 5 were of other races. Table III (vi) shows that the Negroes are relatively more advanced and have relatively less retardation than the Indians and Europeans: the numbers are, however, too small for statistical analysis.

Toxaemia of pregnancy and hypertension. All 31 mothers in this group had a diastolic blood pressure of 90 mmHg or more, in 22 there was proteinuria and in 18 oedema. Table III (vii) suggests relatively more retarded ossification in relation to toxæmia and hypertension, but numbers are small and not significant. 21 of 31 babies in this group were small-for-dates. It is difficult to relate any retarded ossification to the degree of toxæmia but some features are suggestive: 5 of 8 retarded cases occurred with maternal diastolic blood pressures of more than 115 mmHg compared with 6 of 23 cases with normal or advanced ossification. Caesarean section for fulminating pre-eclampsia was considered necessary for 5 of the 8 retarded cases compared with 6 of the 23 other cases.

Parity. Though there is no significant difference when ossification is correlated with the parity of the mothers, Table III (viii) suggests a greater percentage of advanced cases associated with primiparae and of retarded cases with multiparae.

Maternal age. Table III (ix) shows maternal age divided into three groups of 16–24, 25–34, and 35–46 years. The differences are not significant, but some increase of retarded ossification is suggested with increasing maternal age.

No significant differences were found in ossification on comparing (a) fresh and macerated stillbirths, (b) selected normal and excluded cases,

and (c) cases with acceptable and uncertain menstrual dates. Analysis of cases according to primary necropsy diagnoses reflected the features described above.

Discussion

Ossification centres are formed by endochondral ossification which has been mostly studied in the epiphyseal plates of long bones (Sissons, 1971). The process is considered to be largely autonomous in determining the onset and rate of bone development, but it is also influenced by nutritional and endocrine factors which may operate through the mother, placenta, or fetus. Ossification centre development may have a primary genetic control accounting for individual variation for race and sex differences and abnormalities related to congenital malformations. Delayed centre development may result from nutritional deficiencies acting via the mother and placenta as suggested in small-for-dates babies and multiple births. Hormonal control is also probably of major importance and involves the pituitary, thyroid, adrenal glands, and gonads as well as the placenta: evidence is accumulating that fetal endocrine tissues have some degree of independent physiological activity (Jost, 1969). Hormonal changes may also provide a means by which genetic variation is effected.

Male and female. Pryor (1905, 1923) first recognized the sex differences in ossification centre development in the wrists of children and later in the fetal skeleton. This relation to sex in the newborn has been reviewed by Christie (1949) and is supported by his own analysis of 10 ossification centres in 1112 newborns.

Intrauterine growth retardation. The relative retardation of secondary ossification in fetal malnutrition was reported by Scott and Usher (1964) using proximal tibial and distal femoral centres seen in knee radiographs at term. Wilson, Myers, and Peters (1967), using fibula length and ossification centre development in a study of small-for-dates babies, found shorter bone length and retarded ossification. They were also able to show that the postnatal fibular growth rate was similar to that of normal babies after birth but remained poor when low birthweight was associated with congenital lesions.

Multiple births. The number of babies born from multiple pregnancies is small in this series, but the overall range of ossification is significantly

broader than that of the singletons. There was some increase of advanced and more especially of retarded development, but a larger proportion of the small-for-dates babies from multiple pregnancies might be expected to fail to survive. There were some differences in the extent of ossification in the paired cases available in the present study. Similar features have also been reported by Cope and Murdoch (1958), who found a wide variation in centre development in twin pairs, more advanced in the female than the male and in the heavier than the lighter twin.

Congenital malformations. These showed a relatively broad spectrum of ossification with a significant increase of advanced and retarded cases. Marked retardation of centre development was seen in babies of low birthweight associated with trisomy D and E and also in thanatophoric dwarfism, as might be expected with a primary defect of long bone development. Of special interest was the finding that a large proportion of anencephalic fetuses showed significantly advanced ossification: 8 out of 20 were advanced while only 1 was judged retarded. Russell and Rangecroft (1969) have also reported accelerated bone maturation in association with anencephalus. There is evidence that pituitary growth hormone increases bone growth in dimension whereas thyroxin produces advanced maturation in endochondral calcification (Ray *et al.*, 1954; Van den Brande *et al.*, 1973). Such a discordant hormonal effect may account for relatively advanced ossification in the small skeleton of the anencephalic fetus in whom there is a normal thyroid but a major defect in the hypothalamus and pituitary.

Race. Racial differences did not reach statistical significance in the present series, though there was a suggestion of relative acceleration in the ossification of Negro babies. Hess and Weinstock (1925) first reported more rapid development of secondary bone centres in term Negro newborn infants as well as a relation to sex in a radiographical study of carpal bones. The same relatively advanced development in the Negro was reported by Dunham, Jenss, and Christie (1939) in a study of the cuboid bones. Other ethnic variables have also been suggested from Malaysia with increasingly advanced secondary ossification in Chinese, Malays, Indians, and Caucasians, respectively (Chan and Khoo, 1965; Chan, Ang, and Soo, 1972).

Toxaemia of pregnancy. Though there appears to be some retardation of secondary

ossification in association with toxaemia of pregnancy and hypertension in this series, the numbers do not reach statistical significance. Hartley (1957) reported retarded ossification with maternal toxaemia of pregnancy, but this was not confirmed by Russell and Rangecroft (1969). These differences may be due to the populations studied: the small growth-retarded baby is more likely to come to necropsy.

Parity and maternal age. There appears to be some retardation of centre development with increasing parity and increasing maternal age in the present series of cases, but the differences do not reach statistical significance. Christie *et al.* (1941), in a study of the cuboid bone of 1107 surviving newborns, came to the opposite conclusion and considered that ossification was accelerated with higher parity and in older mothers: they stressed that these relations only applied in uncomplicated pregnancies. Our present data are based on pathological material with a high incidence of small-for-dates and malformed babies. Pryor (1908), however, considered that a baby of a primipara was relatively more advanced in carpal bone centre formation than the baby of a multipara.

Maturity estimation. Secondary ossification centres are of limited value in estimating maturity because of the wide range at any one period of gestational age. For example, two centres confined to the os calcis and talus were found between 23 and 40 weeks in the 164 selected cases (Table I). The total or os calcis diameter measurements showed a range of 2 SD of about 8 weeks. At the critical time for induction of labour, 35–36 weeks' gestation, any one of four stages (1 to 4) of development were found. The proximal femoral epiphysis (stage 3), normally seen first at 35 to 36 weeks, sometimes appeared as early as 29–30 weeks.

The wide gestational range for the appearance of the distal femoral centre coupled with the difficulty of *x*-ray identification *in utero* make this method for estimating the maturity of the baby before delivery unreliable. Schreiber, Nichols, and McGanity (1963) reported that where radiographs were taken *ante partum* and shortly afterwards, *post partum*, the distal femoral epiphysis was missed in 44 (20%) of 217 babies. Dee *et al.* (1966) have reviewed the wide differences stated in published reports for the time of appearance of ossification centres and concluded from their own series of cases that radiographs were unsatisfactory in assessing gestational age.

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