ANNALS OF HUMAN BIOLOGY, 1975, VOL. 2, NO. 3, 227–234

The effect of parity on placental weight and birth weight: Interaction with placental alkaline phosphatase polymorphism

RANAJIT CHAKRABORTY
Center for Demographic and Population Genetics, University of Texas

S. R. DAS, MONAMI ROY, B. N. MUKHERJEE and S. K. DAS
Human Genetics and Anthropometric Research Units, Indian Statistical Institute, Calcutta

[Received 20 May 1974; revised 17 June 1974]

Summary. The effect of parity on placental weight and birth weight is examined through a series of birth records from an Indian population in Calcutta. Placental weight and birth weight increase with parity, the maximum increment occurring between parities 1 and 2. This is compatible with a hypothesis of sensitization of the mother to foetal, paternally derived, antigens.

The three common placental alkaline phosphatase enzymic genotypes have no effect on determining foetal development.

1. Introduction

It is well established that birth weight increases with parity of the mother, at least initially, in man as well as in other mammals (Karn and Penrose, 1951; Millis and Seng, 1954; Neel and Schull, 1956; Jayant, 1966). More recent studies indicate that the effect of parity is more important than that of maternal age and furthermore the effects are similar on placental weight and birth weight (Penrose, 1961; Warburton and Naylor, 1971).

As a mechanism of such effects of parity upon placental weight and birth weight, it has been suggested that with increasing parity the mother develops an increasing sensitization to paternally derived histocompatibility antigens. The effect of the antigenic dissimilarity of a foetus and its mother on placental weight and birth weight has been demonstrated in recent years through experiments with mouse and other mammals (e.g., Billington, 1964; James, 1965, 1967). Though the evidence of such maternal–foetal discordance and its effect on placental weight and birth weight in humans is relatively scanty, it is reasonable to assume that such sensitization can stimulate placental as well as foetal growth in humans in the same way as in mice. Warburton and Naylor (1971) attempted to test this hypothesis indirectly through examining a large series of birth weights from the United States of America.

In the present study we attempt to verify their findings from a series of birth records from two hospitals in Calcutta during 1968 and 1969.

2. Material and methods

The data for the present analysis come from a study of the possible physiological effects of the differential enzymic activity of the three placental alkaline

phosphatase alleles PI^{S}, PI^{F} and PI^{I}. During the eight months of the survey, all births (about 1600) were recorded from Baranagore Municipal Maternity Hospital and R. G. Kar Medical College Hospital of Calcutta, India. However, some pregnancies were subsequently excluded from analysis if (i) foetal death occurred, (ii) birth was multiple, (iii) delivery was by Caesarian section, and/or (iv) the mother had shown evidence of diabetes or thyroid disease. Since the parents mostly come from the local population where inbreeding is practically absent (Sanghvi, 1966), it is assumed that in no case are the parents or grandparents of the child related. Whole placental weight was measured shortly after each delivery and small portions of membrane-free placental tissues were immediately dissected and stored at −20°C. Extracts from these tissues were prepared afterwards to determine the placental alkaline phosphatase genotypes. Procedures for the preparation of extracts, electrophoresis and identification of the banding patterns are described in Das, Mukherjee and Das (1970 a, b, 1974) and Blake, Kirk and Matsumoto (1969).

All of the laboratory work was done at the Human Genetics Research Laboratory of the Indian Statistical Institute, Calcutta, with occasional reference to Dr. R. L. Kirk's Laboratory at Canberra for confirmation of some rare phenotypes.

Birth weights and some other body measurements (e.g., crown-rump length, supine length and head circumference) were obtained within 24 h of birth by our survey team. Maternal age, parity of birth and other pre-pregnancy medical and socio-economic observations were recorded.

3. Results

Effect of placental alkaline phosphatase genotypes on other parameters

As has been mentioned, the main purpose of the present survey was to look for possible physiological effects of the three most common allelic types of this particular enzyme. In all, about 11 phenotypes were specifically identified. Of these, only three genotypes, S_1S_1, S_1F_1 and S_1I_1, were found to have sufficient numbers for further perusal. The frequencies corresponding to these three genotypes and those for the eight remaining phenotypes are shown separately for the two hospital samples in table 1. More detailed studies of the gene frequencies and their variations according to the different caste groups are described elsewhere (Das *et al.*, 1970 a, b, 1974). Thus, it is seen that, out of a total of 1392 otherwise suitable births, 1225 belonged to one or another of the above three genotypes. These records alone were used in this analysis.

Hospital	Sample size	Common phenotypes			Other phenotypes*
		S_1S_1	S_1F_1	S_1I_1	
Baranagore Municipal Maternity	600	330	154	54	62
R. G. Kar Medical College	792	445	163	79	105
Total	1392	775	317	133	167

*Includes phenotypes: F_1F_1, I_1I_1, F_1I_1, S_1S_2, S_1S_3, F_1S_2, I_1S_2 and F_1S_3 with frequencies 36, 7, 29, 43, 34, 8, 3 and 7 respectively, in the total sample.

Table 1. Distribution of common placental alkaline phosphatase types collected from two hospitals in Calcutta.

It should be noted that each genotype considered here has one Pl^{s} allele; the other allele being Pl^{s}, Pl^{s} or Pl^{f}. The activity ratios among these three alleles are 0·90 : 0·81 : 0·33, in placenta (Beckman, 1970). This differential enzyme activity does not result in any change in placental weight and birth weight (table 2), and there is no association of genotype with birth weight and placental weight. Table 2 also presents the average maternal age and parity for these three groups along with their standard errors. The three groups are homogeneous with respect to these parameters, suggesting that the differential enzymic activity has no significant effect on birth weight or placental weight of the child. We, then, combined these three groups to study the effects of parity and maternal age on birth and placental weight.

Genotype	Birth weight (g)	Placental weight (g)	Parity	Maternal age (years)
S_1S_1	2630 ± 64	549 ± 14	3·07 ± 0·10	24·80 ± 1·14
S_1F_1	2532 ± 53	531 ± 12	2·99 ± 0·11	24·69 ± 1·07
S_1I_1	2517 ± 52	517 ± 17	2·97 ± 0·09	24·23 ± 1·09
All combined	2572 ± 59	528 ± 13	3·01 ± 0·06	24·16 ± 0·79

Table 2. Average birth weights, placental weights, parity and maternal ages and their standard errors for the three placental alkaline phosphatase genotypes.

Maternal age	Parity						
	1	2	3	4	5	6	7+
Under 21							
Mean	492	529	563	450	0	0	0
SD	109	96	119	0	0	0	0
N	86	46	11	1	0	0	0
21–25							
Mean	539	547	516	567	542	525	600
SD	123	140	123	101	76	43	0
N	46	53	46	19	10	4	1
26–30							
Mean	516	538	530	531	526	557	578
SD	97	114	93	148	85	124	102
N	9	17	26	27	21	17	14
31–35							
Mean	0	625	510	533	442	531	472
SD	0	25	174	100	82	128	121
N	0	2	5	6	7	8	10
36–40							
Mean	500	500	600	0	575	466	559
SD	0	0	0	0	103	60	70
N	1	1	1	0	4	6	11
Over 40							
Mean	0	0	0	0	0	0	0
SD	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0
Total*							
Mean	508	543	525	540	521	534	541
SD	115	121	117	128	92	112	107
N	143	123	92	54	43	36	37

*Including unknown maternal ages.

Table 3. Placental weight in grams by parity and maternal age in the total sample.

Maternal age	Parity						
	1	2	3	4	5	6	7+
Under 21							
Mean	2456	2581	2627	2383	2725	0	0
SD	425	398	246	332	475	0	0
N	186	87	24	6	2	0	0
21–25							
Mean	2458	2580	2580	2564	2614	2383	2735
SD	455	371	412	423	475	512	58
N	90	134	103	51	25	6	4
26–30							
Mean	2395	2505	2682	2701	2641	2692	2789
SD	337	424	381	379	397	490	348
N	27	42	61	60	57	34	31
31–35							
Mean	2725	2705	2546	2718	2446	2672	2557
SD	275	272	456	478	349	335	387
N	2	8	15	17	15	15	22
36–40							
Mean	2205	0	2470	2250	3077	2505	2733
SD	155	0	290	0	727	483	379
N	2	0	3	1	7	10	24
Over 40							
Mean	0	2000	0	2250	2675	0	2640
SD	0	0	0	382	175	0	608
N	0	1	0	4	2	0	5
Total*							
Mean	2456	2569	2613	2624	2638	2627	2691
SD	430	389	387	423	449	467	391
N	319	281	215	141	113	67	89

*Including unknown maternal ages.

Table 4. Birth weight in grams by parity and maternal age in the total sample.

Effect of parity on birth weight and placental weight in the total sample

Tables 3 and 4 show the birth weight and placental weight statistics for the total sample by parity and maternal age. The reduced sample size for the placental weight study (table 3) is due to the fact that there were only 528 records of placental weight, for in nearly 57 per cent of the cases the total placental weight could not be recorded. In both tables, the major concentration of information is in cells near the descending diagonal of each table. This is due to the high correlation of parity with maternal age ($r=0{\cdot}66$, $P<0{\cdot}0001$).

The relative roles of parity, maternal age and genotype in controlling the variability of placental weight and birth weight were examined by a detailed analysis of covariance in these tables. Since the shape of the curve relating birth weight and placental weight to parity was of special interest because of its relevance to the sensitization hypothesis, quadratic and higher order effects of parity and maternal age were also considered in the regression analysis. Maternal age groups were coded as 1 through 6; although the extreme groups are formally open-ended. However, as reported by Warburton and Naylor (1971), age distributions are not seriously distorted by such codes. The parities were considered as they appeared with the exception that the 7+ group is coded as parity 7. The three genotypes are coded as 1, 2 and 3 for S_1F_1, S_1S_1 and S_1I_1, respectively.

Source	Sum of* squares	d.f.	Mean* squares	*F*-ratio	*P*	Regression coefficient
Total regression:	7791	7	1113·0	26·1	<0·0001	
Genotype	51	1	—	1·2	0·2<*P*<0·25	1·94 ± 1·13
Parity	4896	1	—	115·0	<0·0001	78·55 ± 9·44
Parity squared	704	1	—	16·5	<0·0001	−11·63 ± 2·47
Maternal age	166	1	—	3·9	0·04<*P*<0·05	−2·61 ± 1·26
Maternal age squared	421	1	—	9·9	<0·0001	−9·81 ± 2·13
Genotype × Maternal age	833	1	—	19·6	<0·0001	26·61 ± 4·89
Parity × Maternal age	720	1	—	16·9	<0·0001	17·75 ± 3·97
Deviations	4248	118	36·0	0·8	>0·5	—
Error	17889	402	44·5	—	—	—

* In thousands.

Table 5. Analysis of covariance for placental weight.

Source	Sum of* squares	d.f.	Mean* squares	*F*-ratio	*P*	Regression coefficient
Total regression:	1711	7	244·4	57·6	<0·0001	
Genotype	5	1	—	1·2	0·20<*P*<0·25	1·57 ± 0·99
Parity	1291	1	—	304·3	<0·0001	34·53 ± 6·94
Parity squared	53	1	—	12·5	<0·001	−6·84 ± 1·73
Maternal age	15	1	—	3·5	0·05<*P*<0·10	−1·99 ± 1·07
Maternal age squared	62	1	—	14·6	<0·001	−10·53 ± 2·79
Genotype × Maternal age	154	1	—	36·3	<0·0001	24·86 ± 4·93
Parity × Maternal age	131	1	—	30·9	<0·0001	19·51 ± 3·97
Deviations	658	118	5·6	1·4	0·025<*P*<0·05	—
Error	4506	1099	4·1	—	—	—

* In hundreds of thousands.

Table 6. Analysis of covariance for birth weights.

Tables 5 and 6 present the analysis of variance components. Only statistically significant components are shown in the tables with the exception of genotypes. The reason for keeping this component in the tables is to show that enzymic activity does not yield any significant variation in the average birth or placental weights. The other conclusions reached from these tables are in agreement with Warburton and Naylor's (1971) findings. However, in the present series we find that the linear effect of maternal age cannot be totally neglected, although it is only marginally significant in the regression with placental weight (table 5). The linear effects of parity and maternal effects are positive whereas the parabolic effects are seen to be negative. Thus, the negative second derivative of the curve is suggestive of the greatest increment between parities 1 and 2.

Although the main effect of genotype is statistically insignificant, its interaction with maternal age is found to be highly significant ($P<0{\cdot}01$, in both cases). This finding, however, is not very clear from a biological viewpoint. In table 5, the 7 degrees of freedom for the total regression accounts for 65 per cent of the sum of squares among 126 groups, whereas in table 6, for birth weights, regression explains 72 per cent of the total variations in the sample. This suggests that

extraneous variables do not account for a great proportion of heterogeneity in the material.

It would have been interesting to compare the successive pregnancies in the same woman which could provide a test of the hypothesis that sensitization of women to foetal antigens leads to an increase in foetal weight. But these data are not available. We also need records on successive pregnancies for women who have changed mates meanwhile. But such situations are very rare in the middle socio-economic class of this Indian community. However, a comparison of the average increments between successive pregnancies, as shown in table 7, show that only the increments between parities 1 and 2 are statistically significant. The same trend is seen for birth weight as well as placental weight.

	Birth weight	Placental weight
Between parities 1 and 2	113±33**	35±15*
2 and 3	44±35	−18±16
3 and 4	11±44	15±21
4 and 5	14±55	−19±22
5 and 6	−11±71	13±23
Average of rows 2 to 5	15±26	−2±10

* Significant at 5 per cent level ($0{\cdot}01<P<0{\cdot}02$)

** Significant at 1 per cent level ($P<0{\cdot}001$)

Table 7. Average increments in birth weight and placental weight (in grams) between two successive pregnancies and their standard errors. (Increment = later minus earlier.)

4. Discussion

Although it is known that male babies have larger birth weights and placental weights than their female counterparts, we have ignored the sex effect in the analysis. This can have two major consequences. First, the heterogeneity due to a possible sex effect could have elevated the error mean squares in tables 5 and 6, and thus the F ratios attributed to the different sources could have been underestimated. However, this did not change the picture substantially when the analysis of variance for birth weight was done separately for the sexes (not shown here). The main thrust of the study (i.e., the statistically insignificant effect of placental alkaline phosphatase enzyme activities on foetal weight) remains, therefore, unaltered. The conclusions obtained from the significant F values (in tables 5 and 6) would have been more prominent had the sex effect been taken into account. Second, in table 7, it is possible that chance variation in sex of two successive births might be responsible for the differences in comparing parity 1 and 2 and two successive parities of higher order. But, as there is no definite evidence of dependence of secondary sex ratio (sex ratio at birth) on parity, we assume that the chance variation in sex of successive births had the same effect for all comparisons.

As is seen in most studies, birth weight and placental weight are similarly affected at birth order, and thus the inter-relationship between these two variables may be worth studying. The present series of 528 infants on which data on both variables are available gives a correlation coefficient of 0·591 ($P<0{\cdot}0001$). The

correlation coefficient is seen to be homogeneous in all the three alkaline phosphatase genotypes. However, some studies report that the relationship between these two variables may also be curvilinear (Sedlis, Berendes, Kim *et al.*, 1967) in normal pregnancies. Whatever be the relationship, it is not clear at this stage whether the strong association between placental weight and final foetal weight is due to a primary effect of placental size on foetal growth or only to the common genotype and environment of the two systems.

The present series, therefore, is compatible with the hypothesis that the relationship between placental weight, birth weight and parity is due to maternal sensitization to paternal antigens as tested by Warburton and Naylor (1971). However, the role of the placental alkaline phosphatase enzymic types in determining foetal growth is found to be statistically insignificant. Studies of the ABO blood group and placental weight or birth weight also resulted in little evidence concerning the role of maternal–foetal immunological differences on these two variables (Jones, 1968; Gleason and Murray, 1967). In view of this, our negative result insofar as enzyme type is concerned is not surprising since recent studies by Bottini, Lucarelli, Pigram *et al.* (1972 a, b) suggest that the placental alkaline phosphatase polymorphism is also associated with the ABO system (and possibly also with the Rh system) during intrauterine life. In an earlier study with Swedish data, however, significant association of placental weight with the placental alkaline phosphatase genotypes is reported when the variations due to factors like birth weight were not accounted for (Beckman, Beckman and Mi, 1969).

Acknowledgments

This project was supported by the research facilities of the Indian Statistical Institute, Calcutta. We are indebted to Professors C. R. Rao and R. L. Kirk for their advice and encouragement. During the initial planning and initiation of the project we received active participation of Professor R. L. Kirk and full cooperation of his laboratory at Canberra. We are thankful to Mr. N. M. Blake for his active assistance from Canberra. The cooperation of the authorities of Baranagore Municipal Maternity Hospital, Dr. C. S. Dawn (Professor of Gynecology and Obstetrics, R. G. Kar Medical College) and Dr. A. Paul is acknowledged. The analysis and preparation of the paper was supported by a grant from the U.S. National Institutes of Health to R. Chakraborty. We also thank Professor W. J. Schull for his comments and criticisms on a draft of this paper.

References

Beckman, G. (1970). Placental alkaline phosphatase, relation between phenotype and enzyme activity. *Human Heredity*, **20**, 74–80.

Beckman, L., Beckman, G., and Mi, M. P. (1969). The relation between human placental alkaline phosphatase types and some perinatal factors. *Human Heredity*, **19**, 258–263.

Billington, W. D. (1964). Influence of immunological dissimilarity of mother and foetus on size of placenta in mice. *Nature*, **202**, 317–318.

Blake, N. M., Kirk, R. L., and Matsumoto, H. (1969). Placental alkaline phosphatase types in Japanese. *Japanese Journal of Human Genetics*, **13**, 243–248.

Bottini, E., Lucarelli, P., and Gloria, F. (1972 a). Placental alkaline phosphatase and ABO system polymorphisms: Analysis of relationships among gene frequencies in human populations. Further evidence at the population level for an interaction between the two polymorphisms. *American Journal of Human Genetics*, **24**, 505–513.

Bottini, E., Lucarelli, P., Pigram, P., Palmarino, R., Spennati, G. F., and Orzalesi, M. (1972 b). Interaction between placental alkaline phosphatase and ABO system polymorphisms during intrauterine life. *American Journal of Human Genetics*, **24**, 495–504.

Das, S. R., Mukherjee, B. N., Das, S. K., Blake, N. M., and Kirk, R. L. (1970 a). Placental alkaline phosphatase types in Calcutta. *Japanese Journal of Human Genetics*, **15**, 155–158.

Das, S. R., Mukherjee, B. N., and Das, S. K. (1970 b). The distribution of some enzyme group systems among Bengalis. *Indian Journal of Medical Research*, **58**, 866 875.
Das, S. R., Mukherjee, B. N., and Das, S. K. (1974). Caste variation in the distribution of placental alkaline phosphatase genes among the Hindus of West Bengal. *Annals of Human Biology*, **1**, 65–71.
Gleason, R. C., and Murray, J. E. (1967). Report from kidney transplant registry: Analysis of variables in the function of human kidney transplants. *Transplantation*, **5**, 343–359.
James, D. A. (1965). Effects of antigenic dissimilarity between mother and foetus on placental size in mice. *Nature*, **205**, 613–614.
James, D. A. (1967). Some effects of immunological factors on gestation in mice. *Journal of Reproduction and Fertility*, **14**, 265–275.
Jayant, K. (1966). Birthweight and survival: A hospital survey repeated after 15 years. *Annals of Human Genetics*, **19**, 367–376.
Jones, W. R. (1968). Immunological factors in human placentation. *Nature*, **218**, 180.
Karn, M. N., and Penrose, L. S. (1951). Birthweight and gestation time in relation to maternal age, parity and infant survival. *Annals of Eugenics*, **16**, 147–164.
Millis, J., and Seng, Y. P. (1954). The effect of age and parity of the mother on birthweight of the offspring. *Annals of Human Genetics*, **19**, 58–73.
Neel, J. V., and Schull, W. J. (1956). *The Effects of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki*, pp. 131–150. Washington, D.C.: National Academy of Sciences Publication No. 461.
Penrose, L. S. (1961). Genetics of growth and development of the foetus. In *Recent Advances in Human Genetics*, ed. Penrose, L. S., pp. 56–75. London: Churchill.
Sanghvi, L. D. (1966). Inbreeding in rural areas of Andhra Pradesh. *Indian Journal of Genetics*, **26A**, 351–365.
Sedlis, A., Berendes, H., Kim, H.-S. *et al.* (1967). The placental weight–birth-weight relationship. *Developmental Medicine and Child Neurology*, **9**, 160–171.
Warburton, D., and Naylor, A. F. (1971). The effect of parity on placental weight and birth weight: An immunological phenomenon? A report of the collaborative study of cerebral palsy. *American Journal of Human Genetics*, **23**, 41–54.

Address correspondence to: Dr. Ranajit Chakraborty, Center for Demographic and Population Genetics, 1100 Holcombe Boulevard, Room 1109, Houston, Texas 77025, U.S.A.

Zusammenfassung. Der Einfluss der Geburtenzahl einer Mutter auf Plazenta- und Geburtsgewicht wird mit hilfe einer Serie von Geburtsdaten einer indischen Bevölkerungsstichprobe aus Kalkutta geprüft. Beide Gewichte steigen mit der Zahl der Geburten an, wobei der grösste Anstieg zwischen der ersten und zweiten Geburt erfolgt. Die lässt sich mit der Hypothese in Einklang bringen, dass die Mutter für die fetalen, vom Vater stammenden Antigene sensibilisiert wird. Die drei üblichen Genotypen des plazentalen alkalischen Phosphatase-Enzyms haben keine Wirkung auf die Fetalentwicklung.

Résumé. L'influence de la parite sur le poids placentaire et le poids de naissance a été recherchée au moyen d'une série de relevés de naissances provenant d'une population indienne de Calcutta. Le poids placentaire et le poids de naissance augmentent avec la parité, l'accroissement maximal survenant entre les parités 1 et 2. Ceci est compatible avec l'hypothèse d'une sensibilisation de la mère aux antigènes fétaux d'origine paternelle.

Les trois génotypes d'enzymes phosphatases alcalines placentaires n'ont pas d'effet sur le développement fétal.