Human Reproduction vol.15 no.1 pp.55–59, 2000

Birth weight and age at menopause in Australian female twin pairs: exploration of the fetal origin hypothesis

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In a twin sample where duration of gestation can be controlled, a specific example of the fetal origins hypothesis concerning association between low birth weight and early age at menopause is explored. The hypothesis is based on the physiologically plausible path from intrauterine growth retardation and reduced numbers of primary follicles to an earlier menopause. The sample comprised 323 Australian female twin pairs where both co-twins had reached menopause naturally and reported on their weight at birth. Regression analysis showed no linear association between the two variables ($P = 0.371$, $r^2 = 0.0009$). Intra-pair differences in age at menopause were investigated in the context of relative birth weight of co-twins. In 265 pairs an intra-pair birth weight difference was reported. In monozygotic (MZ) pairs ($n = 168$) this allowed for control of genetic effects as well as gestation duration. No significant differences dependent on birth weight relative to co-twin were found for age at natural menopause in either MZ or dizygotic (DZ) twin pairs, even in pairs whose birth weights differed markedly. There was some indication that twins with premature ovarian failure were heavier at birth than twins with normal or later menopausal age. We conclude that the hypothesis that lower birth weight is associated with earlier menopause is not supported by our data.

Key words: age at menopause/birth weight/fetal origin hypothesis/twins

Introduction

There is increasing evidence that the development and function of many internal organs in later life is influenced by intrauterine conditions. The fetal origins hypothesis proposes that undernutrition during the intrauterine period, manifest in a low birth weight, programmes the fetus for diseases in adult life (Barker, 1992). The average organ weight of infants who are small for gestational age is proven to be different compared with infants with a normal weight for gestational age (Plank, 1986). Animal studies have shown that intrauterine growth-retarded sheep have a smaller absolute number of glomeruli (Bains *et al.*, 1996). Not only organ structure but also function can be impaired by intrauterine conditions. Infants who are small for gestational age seem to have a higher risk of developing cardiovascular diseases and some of its known risk factors including high blood pressure and glucose intolerance (Ravelli *et al.*, 1998). Evidence supports a causal relationship between follicle depletion and menopause (Gosden and Faddy, 1998). A poor intrauterine growth in late gestation, manifest in shortness at birth, may lead to a smaller peak number of primordial follicles, which in turn may lead to an earlier menopause (Cresswell *et al.*, 1997). Impairment of ovarian development observed in intrauterine growth-retarded fetuses (de Bruin *et al.*, 1998) may also plausibly have implications for onset of menopause. In a twin sample where gestational length can be controlled, the fetal origins hypothesis of birth weight affecting diseases or characteristics in later life (Barker, 1992; Christensen *et al.*, 1995) can be tested. We investigated the association between birth weight (and relative twin–co-twin birth weights) and age at which female twins reached natural menopause. In this model we investigated the hypothesis that lower weight at birth is associated with early menopause.

Materials and methods

Sample

Data were obtained from twins enrolled with the Australian National Health and Medical Research Council (NHMRC) Twin Registry. This volunteer register has more than 27 000 twin pairs enrolled, about 10–20% of the estimated number of pairs in the population. Two main cohorts of twins were recruited: the first between 1980 and 1982 (1979 female–female pairs aged 17–88), followed up until 1996, and a new cohort of 1628 women (aged over 50) recruited between 1993 and 1995. During the period 1980–1996 six longitudinal surveys were carried out by mailed questionnaire requesting information including age at natural menopause (Do *et al.*, 1998). Both cohorts of twins in two of these surveys were asked for information on weight at birth, the first cohort in the first questionnaire mailed in 1980–1982 (Jardine *et al.*, 1984; Martin and Jardine, 1986; Eaves *et al.*, 1989), and the second cohort in the questionnaire mailed in 1993–1995 (Do *et al.*, 1998). Twins from the first cohort who were still participating in twin research and who were aged over 50 years in 1993–1995 were also sent the latter questionnaire and were asked for their own and their co-twin's birth weight.

Overall pairwise response (including all zygosity groups) was 64% for the first questionnaire (Treloar *et al.*, 1992) and 61% for the

second (Kirk *et al.*, 1999). Responses were available from both members of 2460 female–female twin pairs across the two surveys. Birth weight data were provided by both members of 1761 pairs; however by using cross-twin birth weight reports (see below) this number increased to 2170 pairs. Of these pairs, we could attribute reproductive endpoints and endpoint ages for both members of 1939 pairs. In 1041 (53%) pairs both twins were still menstruating, in 94 pairs (5%) one was pre-menopausal and one had reached natural menopause, in 323 (17%, 208 MZ and 115 DZ) both had reached natural menopause and the remaining 481 pairs (25%) reported other combinations of reproductive endpoints, such as hysterectomy prior to menopause in one twin and menopause in co-twin. Therefore 323 twin pairs provided data for menopausal age and birth weight; 75 of these pairs involved a cross-twin birth weight report; and intra-pair birth weight differences were reported in 265 of the 323 pairs.

Measurements

Age at natural menopause was assessed as age at last menstrual period, where menses had ceased at least 12 months previously, and there was no report of hysterectomy, bilateral oophorectomy or hormone replacement therapy (HRT) before menopause, HRT before hysterectomy, or other reason for cessation of menstruation (Do *et al.*, 1998). Twins were asked to report their own birth weight, and that of their co-twin, in pounds (lb) and ounces (oz) (16 oz/lb) in both questionnaires, since the system of measurement in Australia when the twins were born was imperial rather than metric, and the imperial system was the one with which they were most familiar. Weights were converted to grams (g).

Statistical analysis

Data analyses were performed using SAS version 6.11 (SAS Institute Inc, 1997). Twins were considered both as individuals and as members of twin pairs for particular analyses. We restricted our analyses to twins in female–female monozygotic (MZ) and dizygotic (DZ) pairs. Assessment of intra-pair differences in MZ twin pairs controls for genetic or stable social factors (Christensen *et al.*, 1998b) since they can only be due to specific environmental factors, whereas DZ intra-pair differences are additionally influenced by genetic factors. Statistical tests included analyses of variance, regression and correlations.

We used birth weight data from the 1980–1982 report where available, and the 1993–1995 report only if the former information was missing, given an increased probability of recall problems. However, reports of birth weight were highly correlated between these two surveys, with $r = 0.91$ for own and $r = 0.93$ for co-twin's birth weight. The correlation between self-reported birth weight and co-twin's cross-report of twin's birth weight was $r = 0.95$. Consequently, where twins did not provide their own birth weight, their co-twin's cross-report was substituted.

Attribution of reproductive cycle endpoints and censoring are described fully (Do *et al.*, 1998) and Do *et al.* (in press). We selected for analyses only those twins where there was evidence that menopause had been reached without a censoring event such as prior hysterectomy, HRT use, or other reason for cessation of menses.

Results

Mean age at natural menopause was 48.5 years ± 4.9 years (range 27–60, median 50 years). Mean birth weight was 2373 ± 695 g (range 454–5216). DZ co-twins differed in age of menopause by a mean of 4.1 ± 3.7 years and MZ co-twins by 3.2 ± 3.7 years, a significantly shorter mean interval ($P = 0.006$). These relative differences were consistent with genetic influences on timing of menopause (Treloar *et al.*, 1998). Mean birth weight differences were significantly greater for DZ co-twins than for MZ co-twins (339 g compared with 267 g, $P = 0.035$).

Association between age at natural menopause and birth weight was assessed firstly on individual twin data from co-twins in responding pairs. Regression analysis to see whether age at natural menopause varied according to birth weight showed no linear association between the two variables ($P = 0.371$, $r^2 = 0.0009$). We checked for higher-order terms in regression and other non-linear terms to see if the relationships were linear or quadratic but none were significant.

Intra-pair differences in both birth weight and age at menopause were computed. Partial correlations were performed, controlling for effects which were previously identified as significant predictors of age at menopause in a sample including this sub-sample: age, smoking, education level, age at menarche, and parity (Do *et al.*, 1998). Average combined income, self-rated social class, and occupation group were omitted because of their correlation with education level, and because these variables were characterized by higher levels of missing data. Length of oral contraceptive used was also omitted because it was available only for the first questionnaire respondents, and on this sub-set no association was observed. The partial correlation coefficient between the intra-pair differences in birth weight and age at natural menopause for 163 MZ twin pairs (where data were available for all specified predictors) was not significant (partial Pearson $r = 0.08$, $P = 0.320$). Controlling for predictors of natural menopause and genetic effects still left a non-significant and only very modest association between the key variables. The coefficient was even lower when both MZ and DZ pairs were pooled ($r = –0.01$, $n = 248$ pairs).

In order to detect possible effects of pair-wise censoring, we investigated the zygosity breakdown of twin pairs concordant and discordant for menopause. Of the 94 discordant pairs where one twin was pre-menopausal and one post-menopausal, 55 (59%) were MZ and 39 (41%) DZ pairs. This zygosity balance differed from that of the post-menopausal pairs (64% MZ, 36% DZ), where an excess of MZ pairs may have resulted in some underestimation of intra-pair differences in age at menopause.

Mean ages at natural menopause were calculated for twins who were relatively heavier at birth than their co-twin and compared with the mean menopausal age of their co-twins who were lighter, irrespective of the absolute weight. All co-twins whose reported birth weights differed from each other were included in these twin pair analyses. Fifty-eight pairs where co-twins reported the same birth weight as each other were excluded. Mean intra-pair differences in birth weight and in age at menopause according to birth weight differences are shown in Table I. Finally, in order to increase sensitivity and detect any threshold effects, the analysis was restricted to those pairs who differed in birth weight by at least a given amount: 500 g, 400 g, 250 g and 100 g (see Table I). No significant differences were seen, even in a sub-set of co-

Table I. Mean ages at natural menopause for twin pairs with non-zero intra-pair difference in birth weights

	MZ pairs (n = 168)			DZ pairs (n = 97)			Total pairs (n = 265)[a]		
	Lighter	Heavier	P	Lighter	Heavier	P	Lighter	Heavier	P
Birth weight[b]	2136 (640)	2467 (616)	<0.001	2228 (672)	2630 (665)	<0.001	2170 (652)	2527 (638)	<0.001
Age at menopause[c]	48.89 (4.91)	48.49 (4.75)	NS	49.16 (4.81)	49.16 (4.45)	NS	48.99 (4.87)	48.74 (4.64)	NS
Birth-weight difference									
>500 g	49.46 (4.07)	48.27 (4.11)	NS	48.89 (3.48)	50.44 (4.03)	NS	49.23 (3.81)	49.16 (4.18)	NS
No. pairs			26			18			44
>400 g	48.33 (5.41)	48.47 (4.09)	NS	48.35 (4.55)	49.05 (4.98)	NS	48.34 (5.05)	48.71 (4.46)	NS
No. pairs			57			40			97
>250 g	48.77 (5.24)	48.86 (4.16)	NS	48.74 (4.65)	48.44 (4.87)	NS	48.76 (4.98)	48.68 (4.46)	NS
No. pairs			69			50			119
>100 g	48.95 (4.90)	48.58 (4.71)	NS	49.21 (4.81)	49.20 (4.50)	NS	49.06 (4.86)	48.84 (4.63)	NS
No. pairs			134			94			228

Values are mean (SD).
NS = not significant.
[a]Total pairs used for these calculations is smaller because 58 twin pairs with the same birth weights were excluded.
[b]In grams.
[c]In years.

twins whose birth weight difference was over 500 g. Log transformation of age at natural menopause made no difference.

Individual twins with very premature and very late natural menopause (<35 years and >56 years) differed significantly from each other in their mean birth weights (means 2774 g and 2185 g respectively, $P = 0.028$). The direction of difference was contrary to our original hypothesis, as mean birth weight was actually higher in the twins reaching menopause prematurely than in those reaching menopause after age 56 years. In 14 pairs one or both co-twins had reached natural menopause before age 40 years. In only two of the 14 pairs did the co-twin with non-premature age at natural menopause have a higher birth weight than her co-twin. In all other cases birth weight was lower than or equal to that of the co-twin ($P < 0.05$). The mean birth weight of the heavier co-twins differed significantly from the mean birth weight of the lighter co-twins in the latter group ($P = 0.05$), with a mean intra-pair difference of 307 g.

There was a gap of approximately 13 years between first and second reports of birth weight for a sub-sample of 562 twins who responded to both questionnaires. The Pearson correlation coefficient between the two self-reports of birth weight at a 13 year interval was $r = 0.91$. In a smaller sub-sample who had reached menopause naturally ($n = 291$), $r = 0.92$. Reports by twins in the latter sub-sample on their co-twin's birth weight were also very consistent over the 13 year interval ($r = 0.93$).

Discussion

We found no overall association between birth weight difference and difference in age at natural menopause in this sample of Australian twin pairs. By comparing co-twins we found no evidence of a shift in age at natural menopause depending on birth weight. This applied to individual twins as well as MZ and DZ twin pairs. No significant difference in age at natural menopause was seen, even if the difference in birth weight between co-twins was over 500 g. Therefore, our findings do not support the hypothesis that low birth weight results in early menopause.

Although there is still no clinical evidence, there are (mathematical) indications that ovarian oocyte reserve at birth is an important factor with respect to age at menopause (Gosden and Faddy, 1998). If so, our twin data imply that there is no relationship between limited ovarian oocyte content and low birth weight, and that possible disorders in fetal programming, as put forward by Barker (1992), are not involved in reduction of oocyte reserve. It is possible, however, that 'multiple pacemakers' including central nervous system factors are important in determining menopausal age (Wise *et al.*, 1997), hence numbers of follicles are not explanatory *per se*. Alternatively, it may be that there is a relationship between low birth weight and low oocyte reserve at birth, but that the absolute number of follicles has no effect on the age at natural menopause. The rate of follicle loss might be the determining factor of the age at menopause. It is also possible that we cannot observe the effect of a low oocyte reserve at birth on age at menopause in a twin population. Early age at menarche may be a relevant factor also in oocyte depletion; however, a previous analysis of age at menarche in Australian twin pairs found no significant association between menarche interval and birth weight difference in MZ co-twins (Treloar and Martin, 1990).

We found some indication, at least in some twins, that premature menopause may be related to a higher birth weight. Finding a plausible explanation for this is challenging. A recent paper reported that in singletons, premature ovarian failure was associated with shortness at birth resulting in a high Ponderal index (birth weight/length^3), and suggested that shortness at birth may also be an indicator of intrauterine growth deprivation (Cresswell *et al.*, 1997). We had no information on length at birth with which to evaluate this finding. One mechanism involved in determining the number of oocytes in the ovary at birth is the rate of atresia, an apoptotic process which causes a reduction of the original maximum number of oocytes of about 3×10^6 at mid-gestation

to 1×10^6 at birth. Theoretically, disturbances of this mechanism, based on programming defects, could lead to higher oocyte numbers at birth. If conditions like this do exist, we would expect a favourable, extended age at menopause in the lighter born twins rather than the disadvantageous premature ovarian failure in the twins who were heavier at birth.

There was a considerable mean birth weight difference of around 300 g between those twins who reached menopause before 40 years of age and their co-twins with normal menopausal age. This was also the case comparing individual twins with very late and very premature age at natural menopause. On the other hand, we did not find any difference in age at menopause in co-twins who differed substantially in birth weight. It may be that premature ovarian failure, when found in one twin and not in the co-twin, is not just an extreme of normally distributed age at menopause but a separate entity. From this particular situation it seems hazardous to speculate on possible causal relationships between certain morphometric parameters at birth and premature ovarian failure as disease in later life.

Twin studies have the advantage of controlling for gestational age and genetic factors. For example, in one study a negative correlation between birth weight and blood pressure in a group of individual twins disappeared when association between intra-pair twin differences in both variables was tested, controlling for difference in current weight (Christensen *et al.*, 1998b). We were able to control for other known predictors of age at menopause (Do *et al.*, 1998). The female twins in our sample have been shown to be representative of the Australian population on a variety of indicators including age, general level of education and marital status (Baker *et al.*, 1996). Twins have volunteered to participate in medical research in general and are unselected for any particular characteristics, although self-selection might introduce a bias in the target population, the direction of which is unknown. It is possible that adult twins who are part of a registry may over-represent twins of normal rather than extremely low birth weights, due to the fact that both twins have survived and are able to complete and return survey forms.

Methodological constraints may have impeded detection of any association between birth weight and menopausal age. Pair-wise censoring is an issue arising from selection of pairs where both were post-menopausal, and may have contributed to an under-estimation of the intra-pair difference in menopausal age for the sample selected. One might expect an under-estimation of the difference in age at menopause if those pairs who achieved menopause closer to each other were included in the data set for statistical analysis, while others whose ages at menopause were farther apart were censored from the data set. Evidence suggests that age at menopause is more highly correlated in MZ than in DZ twins (Snieder *et al.*, 1998; Treloar *et al.*, 1998; Do *et al.*, in press). In an earlier study we plotted Kaplan–Meier survival curves comparing MZ and DZ twins conditional on the different intervals of age of menopause in the first twin. For the co-twins of twin probands who reached menopause before age 50 years, the MZ co-twins reached menopause earlier than the DZ co-twins. However, as the age at menopause in one's twin increased, the difference between the survival probability of the MZ twins and the DZ twins became smaller (Do *et al.*, in press). Under-estimation may therefore have occurred, but we would not expect the effect to be large.

Decreased power was a significant methodological issue. The sample size was reduced to 265 pairs when only pairs who differed in birth weight and had both reported reaching natural menopause were included in analyses. This meant that standard errors were large. Although the initial data set was large, by selecting only pairs where both had reached menopause and then only those where co-twins differed in birth weight, our power to detect significant differences was very low. Hence, we consider our study an exploration rather than a test of the fetal origins hypothesis. Mean and median ages at menopause were lower in this sub-sample than in the larger sample (Do *et al.*, 1998).

Other limitations of the study require acknowledgement. Medical records were not sought for confirmation of birth weight and data are based on recall. Recall bias or inaccuracy of original information transmitted to twins could affect data on birth weights. However, cross-twin reporting suggested a high degree of consistency in reporting birth weight. Consistency of reporting of age at menopause over time suggests that recall bias was not a severe problem in this sample (Do *et al.*, 1998). There is no reason, however, why the level of one of the key variables should be biased by the level of the other.

Some questions remain about applicability of our findings to singletons, as possibly different mechanisms lead to birth weight variation in twins compared with singletons. Determinants of late gestational intrauterine growth in twins probably differ considerably from singletons (Gedda *et al.*, 1981; Buekens and Wilcox, 1993). Evidence also suggests that maternal smoking is less influential in twins than singletons for infants weighing less than 90% of mean birth weight, and of equal magnitude where infants weighed over 90% of mean birth weight (Rydhstroem and Kallen, 1996). Despite their low mean birth weight, twins tend to have a lower blood pressure compared to singletons at ages 9 and 18 years (Williams and Poulton, 1999). However, no differences in the probability of conception have been observed between twins and singletons (Christensen *et al.*, 1998a), and mortality among twins after age 6 years is no higher than in the general population (Christensen *et al.*, 1995). It is feasible that a different situation exists for twins, and determinants involved in their late gestational growth retardation may well be uninvolved as causal factors of chronic diseases in later life (Barker, 1992).

In summary, our findings do not support the fetal origins hypothesis in relation to any predictive effect of birth weight on age at natural menopause in twins.

Acknowledgements

The study was supported by the Australian Cooperative Research Centre for Discovery of Genes for Common Human Diseases, the Australian National Health and Medical Research Council (NHMRC) grant number 941177. We thank Nirmala Pandeya, John Pearson and Olivia Zheng for research assistance, and Dr Grant Montgomery for critical review of the manuscript. We especially thank the twins for their co-operation.

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Received on June 4, 1999; accepted on October 6, 1999