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Genetic and Environmental Variation in Menstrual Cycle: Histories of Two British Twin Samples

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Abstract. Information about menstrual cycle variables was obtained by questionnaire using 462 female twin pairs. The twins were either members of the Institute of Psychiatry Volunteer Twin Register, or of the Birmingham Population-based Register. The two samples were analysed separately using univariate and multivariate methods so that an independent replication was obtained. Maximum likelihood estimation was used to fit simple models of genetic and environmental variation to these data. The results suggest that age of menarche, menstrual cycle regularity and premenstrual symptom reporting may be heritable, whereas menstrual cycle length is not. The results should be interpreted with caution as not all variables were replicated in the smaller sample, and the method of retrospective menstrual cycle data collection has been questioned.

Key words: Menarche, Menstrual cycle, Twin register, Model fitting procedures, Genetic analysis

INTRODUCTION

This study examined the extent to which genetic factors are important in the timing and expression of menstrual cycle variables. Premenstrual tension, menstrual cycle length and regularity, as well as age of menarche, are all subject to biological and psychological influences. By examining the concordance rates of these variables in identical and non-identical twins, an indication of the importance of the genetic contribution can be obtained.

Variations in the age of menarche have been studied in different parts of the world,

and a number of different explanations have been offered. Socioeconomic background, family size [20], nutrition [19], athletic activities and geographical location [5] have all been found to account for some of the variability reported. However, since menarche is probably the most fundamental of menstrual cycle factors, it has not surprisingly also been found to have a strong heritable component. Family and twin studies have consistently shown that MZ twins tend to be much more similar than DZ twins for the timing of menarche [8,12,17,18,24].

The result of studies of the length and variability of the human menstrual cycle are far less consistent. Although the majority of women questioned retrospectively about the length of their menstrual cycles report a 28-day cycle [4] a divergence of this assumed normal menstrual cycle length is common in prospective studies [14]. Treloar et al [25] found not only that periodicity in human menstruation between women is characterised by variability rather than regularity, but also that the variability pattern changes throughout menstrual life, with each woman adhering to her own central tendency in menstrual interval throughout reproductive life.

Numerous studies have investigated the relationship between psychosocial variables such as anorexia, stress and personality [13], pheromones [15] and menstrual cycle periodicity and variability, but there is to date a striking lack of studies relating these factors to genetic influences.

The complex interplay among internal and external environmental factors related to the menstrual cycle is even more fascinating and well documented in the expression of premenstrual symptoms. The experience of symptoms associated with the premenstrual phase of the cycle are though to be related to hormonal variation between and even within women [22], as well as to cultural beliefs and stereotypes [3,16]. Nevertheless, virtually nothing is known about the extent to which these factors influence each woman's menstrual experience. Premenstrual tension is a menstrual cycle-related mood disorder which is defined as the cyclic occurrence of symptoms that may be of sufficient severity to interfere with some aspects of life and which appear for each individual with a consistent and predictable relationship to menses. Retrospective studies of premenstrual symptomatology have generally reported a higher incidence and severity and have obtained separate categories of factor clusters of symptoms [6,26,27] which have not been replicated in studies incorporating prospective designs [1,2,21]. Unfortunately, despite extensive interdisciplinary research, little is known about the etiology of the premenstrual syndrome. The aim of this study was therefore to provide an update of menstrual cycle histories in two independent British twin populations, and to evaluate the relative importance of genetics to these variables.

METHOD

Design

Menstrual cycle histories were collected retrospectively by post from over 462 female twin pairs, recruited from two twin registers. These two samples were compared, in order to obtain an independent estimate of replicability of these data. Although the value of retrospective data has been questioned, it was impracticable to use yearly diaries for menstrual cycle length and regularity, and daily diaries for premenstrual symptomatology on the

large sample employed in this investigation.

Subjects

The twins were either members of the Institute of Psychiatry Volunteer Register (N=364 pairs) or of the Birmingham Population-based Register (N=98 pairs). Ages ranged from 18 to 45 years.

Data Analysis

Maximum likelihood estimation was used to fit simple models of genetic and environmental variation to these data. Age of menarche was treated as ordinal data because it is unlikely that recall of the event was accurate enough to treat the data as parametric. Hence a threshold model of liability was used to estimate the effect of heritability on these data. Menstrual cycle regularity also provided us with categorical variables and was treated with the same model. Mentrual cycle length and premenstrual tension were continuous data and the model fitting this parametric data provides estimates of the standard deviation (variance). These data were summarised as variance covariance matrices and, in the case of premenstrual tension, were age-corrected.

RESULTS

Subject characteristics between the two samples were analysed using Chi Square statistics. Table 1 shows the mean (SD) and percentage values of these variables. The mean age of London twins is 31 (8.76) with 34 (10.78) for Birmingham ($\chi^2 = 0.00; P < 0.05$). Other sample characteristics evaluated included oral contraceptive use ($\chi^2 = 1.10; P < 0.05$), general health ($\chi^2 = 0.00; P < 0.05$), gynecological problems ($\chi^2 = 0.00; P < 0.05$), depression ($\chi^2 = 1.63; P < 0.05$), anxiety ($\chi^2 = 0.00; P < 0.05$) and medications used presently ($\chi^2 = 2.01; P < 0.05$). Since none of these variables differed statistically between the two samples, they appear to provide a suitable comparison group for each other. The samples were therefore compared separately. The only significant difference

Table 1 - Sample characteristics

	London	Birmingham
N	928	196
Age	31.06 (8.76)	34.00 (10.78)
Parity: MZ	45.1%	61.8%
DZ	30.4%	52.3%
Oral contraceptive	32.9%	20.6%
General good health	95.7%	92.3%
Gynecological problems	30.3%	34.2%
Medications used	16.4%	28.1%
Depression	20.9%	25.0%
Anxiety	23.1%	27.6%

between these samples was in terms of parity ($\chi^2 = 2.01$; $P > 0.05$), with Birmingham providing us with more parous women than the London sample.

The mean age of menarche was 13.12 (3.19) for 618 London twins, with 13.30 (4.64) for 196 Birmingham twins. These means were not statistically different. The results of the maximum likelihood estimation shown in Table 2 show a significant effect of heritability which is replicated in both samples with little variability due to environmental factors. This result was expected, as discussed earlier. The somewhat smaller sample (Birmingham) was therefore residual because it is not explained by heritability.

A similar genetic model was fitted to some of the less well documented menstrual

Table 2 - Age of menarche in both samples

	I	II	III
T1	- 0.27	- 0.29	- 0.29
T2	0.53		
T3	0.50		
T5	0.10		
HL	0.70	0.71	0.72
CL	0.05	0.00	0.00
HB	0.54	0.53	
CB	0.23	0.23	
χ^2	8.10	9.31	10.83
df		7	9

Threshold variables are shown on the verticle axis, with three models for each horizontally. HL and HB are heritability estimates for the London and Birmingham samples, respectively. CL and CB indicate the common environmental estimates for London vs Birmingham, respectively.

cycle events of length and regularity. The following analyses were restricted to twin pairs where none was currently using the contraceptive pill. This resulted in a subsequent loss of 20% Birmingham and 30% London individuals. The results of the reduced sample of menstrual cycle length are shown in Table 3 where it can be seen that common environmental factors account for most of the variability, whereas genetic factors appear to play virtually no role in this. This effect is also replicated in both samples.

A somewhat different and contradictory pattern was obtained for menstrual cycle regularity as can be seen from Table 4. Here the two samples produced opposite effects, with London twins showing a genetic (HL) and Birmingham twins an environmental (CB) effect for regularity of cycles. These results are rather surprising since although no specific hypothesis was formulated – with previous evidence weighting both environmental and biological factors equally – one might nevertheless expect the result of one sample to be replicated in another very similar population. However, as was the case with the results of menarche, the London sample is much larger and should be considered more accurate than the results of the residual smaller Birmingham sample which is expected to have a larger variance.

Table 3 - Menstrual cycle length in both samples

	I	II	III	IV	V
VarL	4.40	4.57	4.47	4.56	4.58
H2 L	0.01	0.00	0.00	0.00	0.00
C2 I	0.41	0.48	0.48	0.46	0.48
VarB	5.08	15.00	4.87		
H2 B	0.00	0.00		0.16	
C2 B	0.61				
χ^2	65.07	67.24	67.17	67.68	68.13
df	6	7	8	8	9

Variance of heritability and environment estimates are presented for London (L) and Birmingham (B) samples separately along the vertical axis. Five models of the estimate of the standard deviations are shown.

Table 4 - Menstrual cycle regularity in both samples excluding pill users

	I	II	III	IV	V	VI	VII	VIII
T1L (MZ)	1.21	1.16	1.21	1.21	1.21	1.16	1.16	1.16
T2B (MZ)	1.07		1.07	1.07	1.07			
T3L (DZ)	1.09		1.10	1.10	1.10			
T4B (DZ)	1.23		1.23	1.23	1.23			
HL	0.33	0.33	0.28	0.33	0.28	0.28		
CL	0.00	0.00	0.00	0.00	0.00	0.00	0.18	
HB	0.00	0.00		0.12				
CB	0.15	0.15	0.00					
χ^2	3.36	4.39	3.86	3.52	3.86	4.93	6.41	8.49
df		3	1	1	2	5	6	7

Threshold variables are shown on the vertical axis with eight models for each horizontally. For London (L) and Birmingham (B) sample separately.

The data shown in Table 5 reflecting premenstrual symptom reporting, suggests that genetic factors influence the reporting of premenstrual symptomatology. Moreover, the effect of heritability is more pronounced in the Birmingham sample than in the London cohort. The table also shows that where the common environment is allowed to vary for the two samples, there is some evidence of this having a contributory effect in the London but not the Birmingham sample.

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Table 5 - Premenstrual tension in both samples, excluding pill users

VarL	14.06	14.92	14.34	14.92	14.05
H2L	0.30	0.48	0.52	0.48	0.00
C2L	0.13	0.00	0.00	0.00	0.00
VarB	17.59		16.24		
H2B	0.80	0.71		0.71	
C2B	0.00	0.00			
χ^2	8.43	14.51	15.91	14.51	24.39
df	6	7	8	8	9

Variance of heritability and environment estimates are presented for London (L) and Birmingham (B). Samples separately along the vertical axis. Five models of the estimates of the standard deviations are shown.

DISCUSSION

The contribution of genetic vs environmental influences on a range of menstrual cycle events have been examined in two independent British twin populations. It was intended that these two samples, which did not differ statistically in terms of age, oral contraceptive use, general health during the past year, gynecological problems, medication usage, depression and anxiety, would be utilised to replicate the results from one to the other. The only relevant variable which did differ between these cohorts was that the number of women who had children was greater in Birmingham than in London. The extent, if any, to which this had an effect on the differences observed between the samples is currently being investigated.

The results of menarche confirm previous findings of the heritability in the timing of this fundamental human menstrual cycle event. Golden [12] also found evidence of a strong genetic component in onset of menarche, as did a number of earlier investigators using twin samples [11,17]. Tisserand-Perrier [24] obtained a 2.2-month difference in MZ and 8.2-month difference in DZ age of menarche. She also notes that, as a result of lower birth rate, twin samples show later development in all cycles of growth, including age of menarche, compared to the normal population. This point is supported by ample evidence from studies of minimum weight for height, in the attainment of an average critical body weight [9,10]. However, although it is probably true to assume that the present results represent the commonly held belief that age of menarche is the result of both genetic and environmental factors [23] the apparently essential factors such as maximal weight and height are less influenced by genetic factors than the age at which it appears [8]. It is therefore expected that chronogenetics, the inheritance of biological time [11], may require extreme environmental effects or severe illness to upset this biological timing.

A somewhat unexpected result was obtained for menstrual cycle length and regularity. Although no specific hypothesis was formulated, there is some evidence suggesting that age of onset of menarche is related to both these variables, with late menarche predicting longer and more irregular cycles [13]. No evidence for this was found in the present study. In fact, the opposite was evident. Menstrual cycle length was found to be accounted for

almost entirely by environmental factors in both samples, whereas regularity of cycles was found to be heritable to some extent in the London, but not at all in the Birmingham sample. This result is somewhat unexpected, since although the direction was not specified, the inconsistency of the results is puzzling. One explanation for this may be that the loss of 20% Birmingham and 30% London individuals (by excluding oral contraceptive users) has reduced the numbers to such an extent that the results of the smaller sample cannot be taken on trust. However, despite this, the genetic effect in the London sample is not entirely explainable on the basis of existing evidence. It is possible that "regularity" is used in a broadly relative sense as has been suggested by others [25], and that these results need confirmation in a prospective study.

Premenstrual tension, as reflected in symptom reporting based on the most recent premenstrual week is found to be largely heritable in the present study. These results pose a number of interesting methodological questions. Firstly, it is possible that MZ twins have a tendency to report symptoms of discomfort in a similar manner, because of the intimacy of their relationship, compared to DZ twins. Secondly, it is possible that all twins report on average a similar range of symptomatology, including a similar level of severity of the occurrence of premenstrual symptoms, as would be predicted by a socio-cultural theory of premenstrual tension. A number of previous investigations using non-twin samples have found stereotyped attitudes to symptom reporting premenstrually in retrospective studies [16], whereas this was not found to be an important bias in prospectively designed surveys [3]. It is therefore clear that, although the present results have been replicated in an independent sample, their validity can best be tested in a follow-up study investigating a smaller number of twins prospectively.

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