The majority of irregular menstrual cycles in adolescence are ovulatory: results of a prospective study

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ABSTRACT

Purpose While ovulation is most likely to occur in adolescent girls with regular menstrual cycles, there are limited data on the incidence of ovulation in girls with irregular menstrual cycles in early postmenarcheal years. The aim of the study was to evaluate the presence of ovulation in healthy postmenarcheal girls with irregular menstrual cycles.

Methods, design and subjects Prospective cohort study over 12 weeks including 40 healthy postmenarcheal girls recruited from the population-based cohort of adolescents from Western Australian Pregnancy Cohort (Raine) Study with irregular menstrual cycles defined by either menstrual cycles <21 days or >35 days in duration or cycle length that varied from month to month by >4 days according to menstrual diaries.

Main outcome measure Ovulation defined by urinary pregnanediol-3α–glucuronide/creatinine measurements higher than three times above minimum value obtained from 12 samples (1 per week).

Results Forty girls (37 Caucasians) with irregular menstrual cycles aged 15.1 (median (IQR) 14.9–15.4) years who were 2.3 (1.9–3.3) years postmenarche were assessed. Urinary pregnanediol-3α–glucuronide/creatinine values identified that 33 girls (82.5%) ovulated during the 3 months of observation and 7 girls had anovulatory cycles. Menstrual diaries collected for a median (IQR) of 159 (137.5–188.2) days showed median minimal and maximum menstrual cycle duration of 24 (11.5–29) and 38.5 (35–48) days, respectively.

Conclusions A large proportion of healthy adolescent girls with irregular menstrual cycles are still ovulating despite irregular and infrequent menses.

What is already known on this topic?

► There is significant menstrual cycle variability during early postmenarcheal years.
► Ovulation occurs most commonly in adolescent girls with regular menstrual cycles.
► Oligoanovulation is most likely to occur in women with irregular menstrual cycles and in girls during early postmenarcheal years.

What this study adds?

► Ovulation occurs in a large proportion of healthy girls with irregular and infrequent menstrual cycles during early postmenarcheal years.
► History of menstrual cycle irregularity should not be used as clinical correlate of oligoanovulation in adolescent girls.
► There is a need to reinforce strategies to prevent unplanned pregnancies in adolescent girls with irregular menstrual cycles during early postmenarcheal years.

INTRODUCTION

It is accepted that there is significant menstrual cycle variability during adolescence and during the perimenopausal period.[1 2] Studies evaluating menstrual cycle variations and ovulation in early to mid-postmenarcheal years have been derived from relatively large cohorts evaluated more than 40 years ago. These report a decrease in menstrual cycle variability over time with the majority of girls achieving regular menstrual cycles 5–7 years after menarche.[3–5] However, this may occur earlier than 3 years postmenarche according to more recent studies and might be related to earlier maturation of hypothalamic pituitary axis.[6–8]

Recent studies report the association between irregular menstrual cycles in adolescence and the presence of abnormalities such as polycystic ovary syndrome during adulthood.[9–11] However, there is limited evidence on menstrual cycle variations and their relation to ovulation patterns in healthy girls during early postmenarcheal years.

Oligoanovulation occurs most commonly in women with irregular menstrual cycles and during the early postmenarcheal years.[3 4 12] Ovulation rates increase postmenarche with reported percentages of 14%–22.9%, 25%–38%, 44.8%–50%, 42.9%–48% and 63.2%–64% in girls who were less than 1 year, 1–2 years, 2–3 years, 3–4 years and 4–5 years postmenarche, respectively.[3 4] While ovulation is most commonly associated with regular menstrual cycles, no studies have evaluated the association between menstrual patterns and objectively measured ovulation in healthy girls with irregular menstrual cycles in the early postmenarcheal years. Therefore, we aimed to evaluate the presence of ovulation in a subset of well-characterised adolescent girls from a population-based

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birth cohort to determine the association between irregular menstrual cycles and objectively determined ovulation. We hypothesised that girls with irregular menstrual cycles were largely anovulatory.

METHODS

Subjects and study design

The Western Australian Pregnancy Cohort (Raine) Study (www. rainestudy.org.au) was formed from a pregnancy cohort study, in which 2900 women were enrolled in a controlled trial by the 18th week of gestation from the antenatal booking clinics.[13] Mothers were enrolled over a total of 30 months commencing in May 1989 and finishing in November 1991. The last children were born in April 1992. The 2868 children who were born to 2804 mothers were retained to form the Western Australian Pregnancy Cohort (Raine) Study. The study aimed to investigate the role of perinatal events on subsequent childhood and adult health. The cohort is unique because detailed antenatal, postnatal and childhood measurements have been made. Cohort follow-up was undertaken at ages 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22 years, making it one of the largest and most closely followed prospective cohorts of pregnancy, childhood and adolescence in the world.

An unselected subset of 230 girls, the majority of whom were at least 2 years postmenarche, as age at menarche had previously been prospectively determined,[14] were recruited for the reproductive assessment studies reported previously.[15 16] The study visit was scheduled for days 2–5 of the menstrual cycle by asking the girls to telephone the research nurse on the first day of menses. This ensured that subjects with regular and irregular menstrual cycles were sampled during the early follicular phase. At this visit, age and personal and family medical histories were recorded. The subject's height, weight, and waist and hip circumference were measured. A subset of 40 girls with irregular menstrual cycles were recruited from this cohort and were included if they were healthy, at least 6 months postmenarche and were not taking any sex steroid hormones or any other medication that interferes with pituitary, ovarian or endometrial function. Irregular menstrual cycles in this study were defined as less than 21 days or more than 35 days in duration or where the cycle length varied from month to month by more than 4 days.[17]

All girls were asked to complete a prospective purpose-designed menstrual diary over 12 weeks and to collect and store in the freezer a morning urine sample once a week for 12 consecutive weeks. The study was approved by the Raine Executive Committee and the Ethics Committee of Princess Margaret Hospital. Girls and their parents/guardians gave written consent.

Sex steroid measurement

Urine samples were immediately frozen ($-20°C$) after collection and then the 12 samples per girl included in the study were returned as a batch for the laboratory for analysis. All urine samples from each girl were initially thawed and evaluated for colour, turbidity, specific gravity, pH, leucocytes and blood to ascertain if they were indeed collected at different times over 12 weeks. Separate aliquots of each sample were stored at $-80°C$ for the subsequent analysis of pregnanediol-3α–glucuronide (PdG) and creatinine.

Urine PdG was analysed using an enzyme immunoassay kit (IM114) from Immunometrics (Beckman, Sydney, Australia). The inter and intra-assay coefficients of variation were both <12% and the assay sensitivity was 0.5 ng/mL. Urine creatinine was measured using a colorimetric assay kit (Cayman

Chemical, Ann Arbor, MI, USA). Each urine PdG value obtained was standardised for each urinary creatinine value measured.

Statistical methods

All urinary PdG/creatinine values obtained from each girl were analysed to calculate the minimum value in the data set and the threshold of three times above the minimum value as proof of ovulation in each girl.[18] Values greater than three times the minimum value for urinary PdG/urinary creatinine on each data set were identified. The presence of at least one value greater than three times the minimum value for urinary PdG/urinary creatinine over 12 weeks was used to define a positive ovulatory pattern. Two or more values and one value greater than three times the minimum value for urinary PdG/urinary creatinine over 12 weeks were classified as persistent and sporadic ovulatory pattern, respectively. Figure 1A and figure 1B are examples of two girls in this cohort with positive ovulation pattern identified by this method. Categorical data were summarised with the use of frequency of distributions. Continuous data were summarised as means and SD or median and IQRs according to normality. SPSS statistical software (V.15.0) was used for data analysis.

RESULTS

Forty adolescent girls (mean age ± SD 15.2±0.5 years, 37 Caucasians, 2 Asians and 1 Polynesian) participated in this prospective study. The mean age at menarche was 12.3±1.2 years. Their mean body mass index (BMI) was 23.6±4.6 kg/m^2 and 11 were classified as overweight (BMI percentile 85%–95%) and 5 as obese (BMI percentile >95%). Their mean waist-to-hip ratio was 0.83±0.1. Urinary PdG/creatinine was measured in 446 urine collected samples over 12 weeks. All girls collected a minimum urine sample required for analysis of PdG/creatinine.

Menstrual diary data were completed by 38 girls and included 204 menstrual cycles (table 1). Five girls had one cycle longer than 60 days and one girl had a cycle longer than 90 days. All girls had irregular menstrual cycles as defined by cycles <21 days (n=15) or >35 days (n=22) in duration; and/or cycle length that varied from month to month by more than 4 days (n=1). Using the definition of irregular menstrual cycles as menstrual cycles <21 days and >45 days,[19] menstrual diaries showed that 26 girls had irregular menstrual cycles.

Urinary PdG/creatinine values identified 33 girls (82.5%) with an ovulatory pattern and 7 girls with an anovulatory pattern (figure 2 is an example of a girl in this cohort with anovulatory pattern) (table 1). Of the girls with positive ovulatory pattern, 27 had a persistent ovulatory pattern (figure 1A is an example of this ovulatory pattern) and 6 had sporadic ovulation pattern (figure 1B is an example of this ovulatory pattern).

Of the 26 girls who had either menstrual cycles less than 21 days or more than 45 days, urinary PdG/creatinine values identified 21 girls (80%) with an ovulatory pattern and 5 girls with an anovulatory pattern. Of these 26 girls, 15 have menstrual cycles less than 21 days (12 with ovulatory pattern) and 11 have menstrual cycles more than 45 days (9 with ovulatory pattern). There were 11 girls with menstrual cycles between 35 and 45 days duration, 10 of which were ovulatory, and 1 girl with menstrual cycles that varied by more than 4 days, which had an ovulatory pattern (figure 3).

DISCUSSION

Irrespective of using a definition of irregular menstrual cycles as being less than 21 days or more than 35 days in duration,
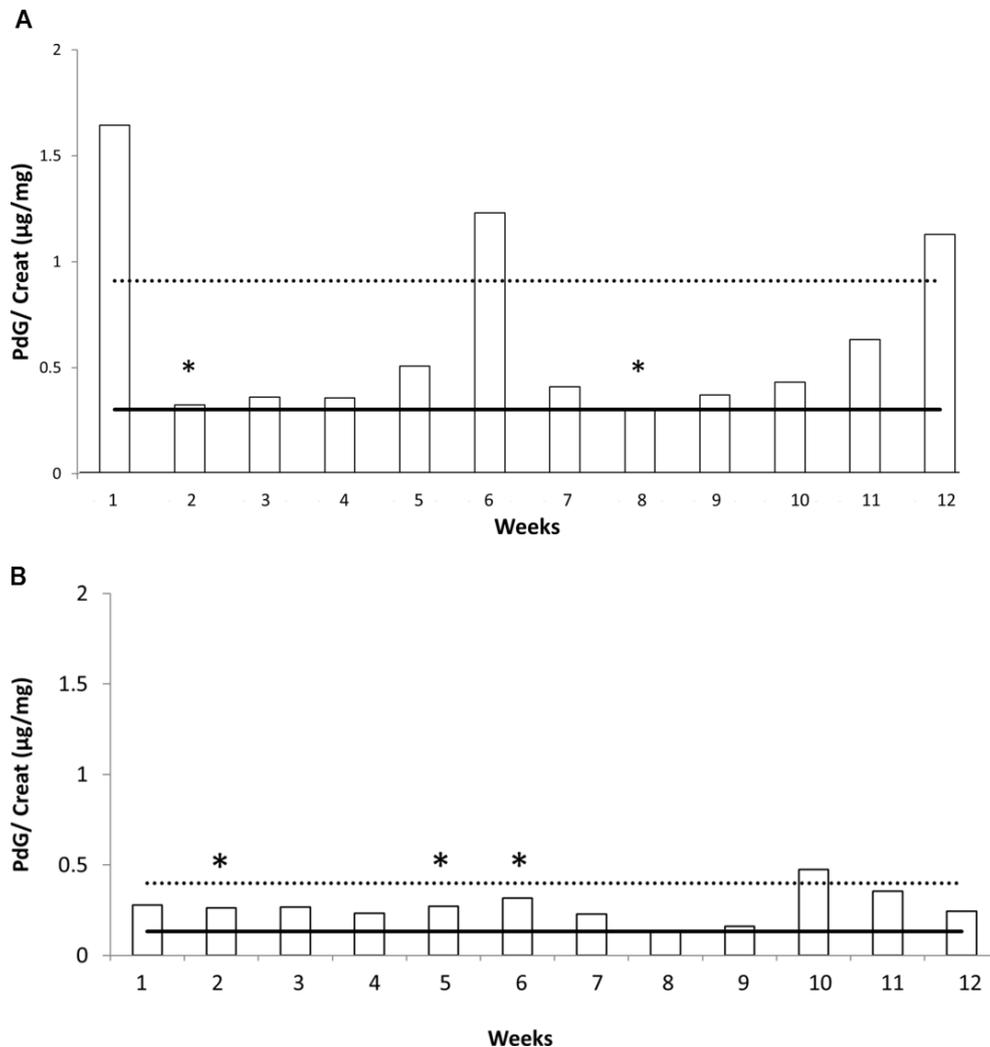
Figure 1 Examples of positive ovulatory patterns according to urinary pregnanediol-3α–glucuronide/creatinine values over 12 weeks. Example of a girl with (A) a persistent ovulatory pattern, with menstruation occurring with 2 weeks subsequent to ovulation. (B) a sporadic ovulatory pattern. Continuous line indicates minimal urinary PdG/creatinine value over 12 weeks. Dotted line indicates 3 times above minimal PdG/creatinine value. * indicates urine sample positive for blood. PdG, pregnanediol-3α–glucuronide.

or which vary from month to month by more than 4 days, or by being defined as less than 21 days and more than 45 days in duration, in the early years postmenarche most healthy girls with irregular menstrual cycles are still ovulating. This suggests that a history of menstrual cycle irregularity should not necessarily be used as a clinical correlate of anovulation or oligoanovulation in this population. Similarly, a history of regular menstruation does not reliably reflect ovulation as healthy adult women with regular menstrual cycles have a prevalence of anovulation up to 18%–30%. This was demonstrated in cohorts of 259 and 3168 women, respectively.[20 21] Anovulation is more likely to occur in younger women who have short (less than 26 days) or long

Table 1 Menstrual diaries data

	All girls (n=40)	Girls with ovulatory pattern (n=33)	Girls with oligoanovulatory pattern (n=7)
Age (years)	15.1 (14.9–15.4)	15.1 (14.3–15.4)	15.0 (14.9–15.2)
Time since menarche (years)	2.3 (1.9–3.3)	2.3 (1.6–3.2)	3.1 (2.1–5.2)
Body mass index (kg/m^2)*	23.3 (20.4–25.6)	22.8 (20.1–24.4)	25.8 (23.7–35.6)
Body mass index z-score*	0.84 (0.13–1.28)	0.69 (0.01–1.13)	1.3 (1.0–2.3)
Number of days recorded	159 (137.2–188.2)	159.5 (140.3–188.3)	154.5 (116.5–189.8)
Number of cycles per girl	5 (4–7)	5.5 (4.0–6.8)	4.5 (4.0–7.3)
Minimal cycle length (days)	24 (11.5–29)	13.5 (24.5–29.0)	18.5 (8.3–27.0)
Maximum cycle length (days)	38.5 (35–48)	37.5 (35.0–47.8)	43.0 (37.8–53.3)
Average cycle length (days)	32 (25–34.2)	32.0 (25.0–34.8)	30.0 (21.8–36.5)

Data are median (IQR).
*p<0.05 between girls with ovulatory and oligoanovulatory patterns.
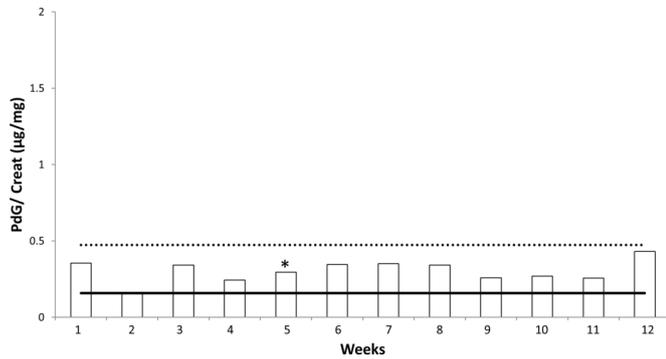
Figure 2 Example of a girl with an oligoanovulatory pattern according to urinary PdG/creatinine values over 12 weeks, despite menstrual bleeding during week 5. PdG, pregnanediol-3α–glucuronide. * indicates urine sample positive for blood

(more than 35 days) menstrual cycles.[22 23] In addition, some girls with regular menstrual cycles during late adolescence are anovulatory.[3 4 24 25] The association between menstrual cycles and ovulation patterns in early postmenarcheal years can be variable during the maturational period of hypothalamic-pituitary-ovarian axis as shown in 10 healthy girls with extensive urine and serum hormonal investigations and intensive follow-up during the first 2 years postmenarche.[8]

The rate of ovulatory cycles in adolescent girls increased with age and the rate of ovulation in our cohort at 1–3 years postmenarche was higher compared with previous reports in the late 1970s including similar numbers of subjects in this particular age group.[3 4] These differences may be methodological, since we performed multiple urinary PdG measurements compared with a limited number of plasma or salivary progesterone levels in older studies.[26] Similarly, the mean age of menarche in the Raine cohort (12.3 years) was younger than that previously reported in the 1970s (13 years), reflecting the well-established fall in age at menarche in many countries over recent decades. Earlier age at menarche may be associated with greater rates of ovulatory cycles.[27] Our ovulatory rates are also higher (82% vs 40%) in comparison to girls of similar age presenting for investigation of persistent irregular menstrual cycles.[28] Healthy girls from the community might have a maturational transitional pattern to normal or adult women ovulation rate up to 90%.[20] Also longitudinal studies have shown a rapid maturation of reproductive axis in healthy girls.[7 8] On the other hand, girls evaluated for persistent irregular menstrual cycles are more likely to have lower ovulation rates, high androgen levels and polycystic ovaries on ultrasound.[10 29]
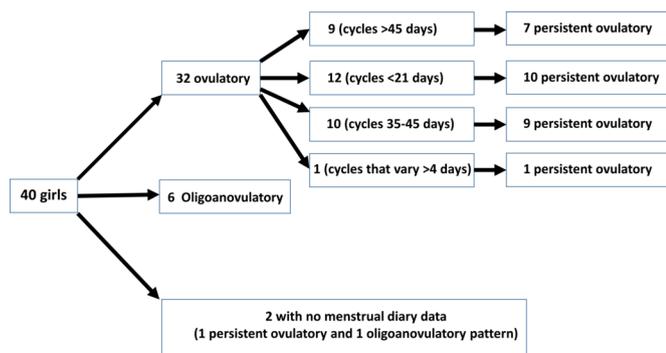

Figure 3 Ovulation patterns.

Urinary and serum sex steroid hormones have been used as alternative methods to evaluate the presence of ovulation.[3 4 8 25 30] Urinary PdG is a water soluble metabolite of progesterone that increases above baseline levels after ovulation (as detected by repeated transvaginal ultrasounds which is the gold standard method). This increment in urinary PdG after ovulation persists for few days making a weekly urinary sample a very feasible and reliable method to assess ovulation which has been repeatedly validated in the literature.[18 31 32] Transvaginal ultrasound is inappropriate in younger adolescent girls, few of whom were sexually active.[33]

Unsurprisingly, as the girls in the study were selected as having irregular menstrual cycles, they had higher BMI and higher prevalence of being overweight or obese in comparison to Australian population of similar age.[34] Additionally, girls with oligoanovulatory patterns had higher BMI compared with girls with ovulatory patterns. This is consistent with previous studies including adolescent girls[9] and large cohorts of young women.[35 36]

Strengths of this study include measurement of ovulation using weekly determinations of urinary excretion of PdG corrected for creatinine for a period of 12 weeks with a high compliance rate. This method can estimate the presence or absence of ovulation with good sensitivity and specificity.[18 31 32 37] A limitation was the small number of anovulatory cycles and the small number of long cycles observed; however, adolescent girls had a reasonable variability in their menstrual cycle length and our mean age at menarche and median menstrual cycle length was comparable to larger cohorts.[38–40] Furthermore, as this study included mainly Caucasian girls within 1–3 years from menarche, these findings should not be generalised to non-Caucasian girls in the immediate postmenarcheal year as these girls are more likely to have higher oligoanovulation rates.[3 4]

In conclusion, this study shows that the majority of girls with irregular menstrual cycles within 1–3 years of menarche are ovulating. Therefore, irregular menstrual cycles in otherwise healthy adolescent girls should not be considered as anovulatory, highlighting the need to reinforce strategies to prevent unplanned and high-risk pregnancies during the early postmenarcheal years even in adolescents with irregular menstrual cycles.

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