Purpose: *This assignment introduces the research of Dr. James Brown.*
Instructions: *Please read the following excerpt and answer the questions.*

Types of ovarian activity in women and their significance: the continuum

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Abstract

BACKGROUND There are many types of ovarian activity that occur in women. This review provides information on the relationship between the hormone values and the degree of biological response to the hormones including the frequency and degree of uterine bleeding. The continuous process is termed the 'Continuum' and is thus similar to other processes in the body.

METHODS This review draws on information already published from monitoring ovarian activity by urinary oestrogen and pregnanediol measurements using timed 24-h specimens of urine. Much of the rationalization was derived from 5 to 6 year studies of girls progressing from childhood to adulthood, women progressing through menopause, and the return of fertility post-partum. During these times, all the reported types of ovarian activity were encountered.

RESULTS All cycle types can be understood in terms of steps in the normal maturation of fertility at the beginning of reproductive life, its return post-partum and its demise at menopause. Each step merges into the next and therefore the sequence is termed the 'Continuum'. Unpredictable movement from fertile to infertile types and back can occur at any time during reproductive life. Stress is a major causative factor. Hormonal definitions for each step, the relevance of the various cycle types in determining fertility and in the initiation of uterine bleeding and the roles of the pituitary hormones in causing them, are presented.

CONCLUSIONS The findings explain the erratic fertility of women and why ovulation is not always associated with fertility. They provide an understanding of the various types of ovarian activity and their relation to pituitary function, fertility and uterine bleeding.

Introduction

The characteristics of the fertile ovulatory cycle are well documented, but much confusion exists concerning the many other, less common, types of ovarian activity in women. Because these are infertile and sometimes associated with erratic bleeding patterns, they are universally classified as 'abnormal'. Furthermore, no unifying concept has been proposed of why they exist during reproductive life. Many gynaecologists still concentrate on regularizing the bleeding patterns without understanding the underlying hormonal environment, either endogenous (ovarian activity) or exogenous. Studies performed ~30 years ago showed that the transitions from the amenorrhoea and infertility of childhood to the fully fertile ovulatory cycle of adulthood, during the return of fertility after child-birth and during its regression at menopause all followed the same sequence or its reverse. The sequence involved a continuous process that included all the types of ovarian activity that have been documented. Furthermore, all the types of ovarian activity could be produced during gonadotrophin therapy. As all the women being treated were aiming at pregnancy, the roles of the two pituitary hormones, follicular stimulating hormone (FSH) and luteinizing hormone (LH), contained in the gonadotrophin administered in causing each cycle type and the fertility potential of each type could be determined. The progression can now be conceptualized as steps progressing from: (i) no ovarian activity, (ii) anovulatory follicular activity with raised constant or fluctuating oestrogen levels, (iii) luteinized unruptured follicle (LUF), (iv) ovulation followed by a deficient or short luteal phase and (v) fully fertile ovulatory cycle, or the reverse of this sequence. Only Type 5 is capable of producing a

continuing pregnancy. Therefore, as all the cycle types are part of a normal process they cannot be considered as abnormal. The studies also provided information on the relationship between the hormone values and the degree of biological response to the hormones, including the frequency and degree of uterine bleeding. The Steps 1–5 are actually a continuous progression from childhood to adulthood beginning with the increasing production of sufficient oestrogen to eventually cause uterine bleeding (menarche). This is followed by the gradual regularization of this process and, importantly, the gradual maturation of the 'ovulatory mechanism' which includes the total process in which LH is released and the subsequent events leading to ovulation. Therefore the process is termed the 'Continuum' and is thus similar to other processes in the body. Because it is a continuous process, each conceptualized step cannot be described in terms of means and standard deviations.

Methods

Assessment of ovarian activity

Ovarian activity was assessed by measuring the cyclic outputs of the two ovarian hormones, oestrogen and progesterone by measuring their principal metabolites in urine. This measurement does not distinguish between whether oestradiol or oestrone is the primary ovarian oestrogen but it is generally considered to be oestradiol (Brown, 1957; Baird and Fraser, 1974). Because of the rapid changes in the secretion of the hormones, particularly just before and after ovulation, when daily changes of 30–50% are usual, it is necessary to monitor ovarian activity frequently, ideally daily.

Long-term studies

The studies of individuals progressing through menarche and menopause were performed using oestrogen methods B and C and the GLC pregnanediol method (B). These studies required up to 5 years of observations in the same individual. Clearly it was not possible to sample ovarian activity daily over this time. Resort was made to weekly urine sampling which always included parts of both the follicular and luteal phases of a cycle. Production of cervical mucus as assessed by the Billings Ovulation Method of Natural Family Planning (NFP) (Billings *et al*., 1974) was recorded daily. Mucus production is a useful self-bioassay of ovarian hormone production and the maximum score (Brown *et al*., 1985) correlates closely with peak oestrogen production (Billings *et al*., 1972). Through knowledge of the mucus scores, times of bleeding and the weekly hormone levels, it was possible to approximately identify the times of ovulation, the oestrogen peak and the pregnanediol rise and maximum.

Short luteal phase

The short luteal phase has already been defined and demonstrated in Fig. 5. Short luteal phases are common during the first cycles post-partum but they also occur sporadically throughout reproductive life. Deficient and short luteal phases can occur in the one cycle and are the most common types of infertile ovulatory cycles. An important finding was that all ovulatory cycles (pregnanediol excretion reaching or exceeding 2 mg/24 h) were followed by bleeding whether the luteal phase was normal, deficient or short, provided the endometrium was responsive to hormonal stimulation, the subject was not pregnant and no blockage was present. This differs from anovulatory cycles where bleeding may or may not follow an oestrogen peak (Fig. 13 in Brown *et al*., 1959).

Stylized patterns for the steps in the continuum

Figure 9A–I demonstrates the patterns in stylized form summarizing the various steps in the continuum. It should be appreciated that each is a step in a continuous process. Possible sequels are shown because it is important that women who are identifying their fertile periods for either pregnancy achievement or avoidance understand that continuation of current patterns of fertility can never be assumed and vigilance is always required to detect the next onset of fertility. The figures progress from no activity (A) which may be interrupted by a return of a fertile ovulation, through anovulatory activity of the fluctuating (B) or constant oestrogen (C) type and progress in that cycle to fully fertile ovarian activity, through a LUF (D) which may be followed in the same cycle by a fertile ovulation, through a deficient (E) or short (F) luteal phase which may, in the next cycle, revert to a fertile ovulatory cycle. The range of values seen during the ovulatory cycle, (G), 10th percentile and (H), 50th percentile and (I) reaching even greater fertility with gonadotrophin therapy.

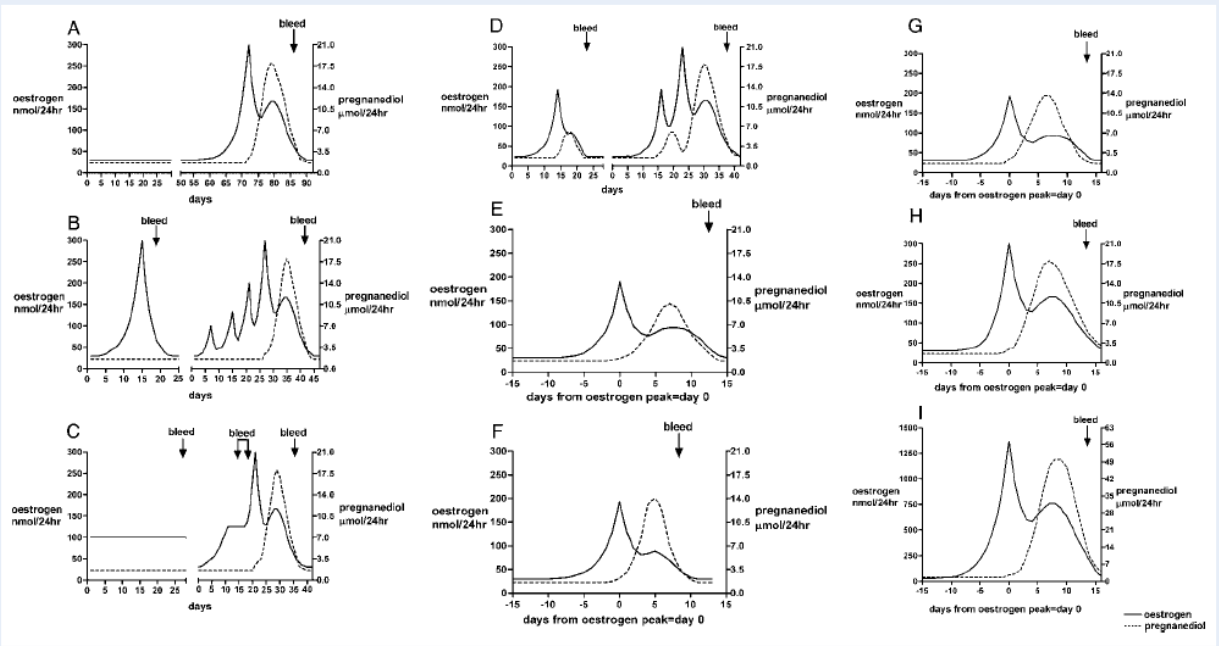

Figure 9 Conceptualized cycles of the continuum. (**A**) Uniformly low TE and pregnanediol values denoting no ovarian activity and amenorrhoea. A fertile ovulatory cycle may follow spontaneously. (**B**) Anovulatory ovarian activity with a sharp oestrogen peak followed closely by oestrogen withdrawal bleeding. Days 30–70, a possible sequel, several anovulatory oestrogen peaks not followed by bleeding which might have been interpreted as ovulatory oestrogen peaks but recognized by absence of a progesterone rise and eventually followed by a fertile ovulation. (**C**) Days 1–30, anovulatory ovarian activity with constantly raised oestrogen excretion and oestrogen breakthrough bleeding. Days 30–70, possible sequel, situation correcting itself and progressing to a fertile ovulatory cycle, the oestrogen breakthrough bleeding then seen as mid-cycle bleeding. (**D**) Days 1–25, a sharp oestrogen peak followed by a LUF follicle followed by bleeding; the pregnanediol values rose temporally but did not reach 2 mg/24 h (9 µM/24 h). Days 30–70, possible sequel, a LUF not followed by bleeding but followed by a fertile ovulatory cycle. (**E**) Ovulation followed by a deficient luteal phase in which the pregnanediol values exceeded 2 mg/24 h (9 µM/24 h) but did not reach 3 mg/24 h (13.5 µM/24 h). Menstruation followed. (**F**) Ovulation followed by a short luteal phase of 10 days or less. The pregnanediol values usually exceed 3 mg/24 h but fall prematurely. Menstruation followed. (**G**) A fertile ovulatory cycle with hormone values at the 10th percentiles. (see Fig. 8). (**H**) A fertile ovulatory cycle with hormone values at the 50th percentiles. (**I**) An enhanced ovulatory cycle produced by gonadotrophin therapy.

The continuum

The various types of ovarian activity reported here are explained as being part of the normal sequence seen during the change from the amenorrhoea of childhood through anovulatory ovarian activity at menarche and the gradual maturation of the ovulatory mechanism to the eventual establishment of the fertile ovulatory cycle. Each stage merges with the next and consequently the process is termed ‘the continuum’. The five conceptualized types are not entities and therefore cannot be grouped as such. Stress of any kind during reproductive life is the most important factor causing ovarian activity to change from the fertile to infertile types. Removal of the stress usually allows fertility to return. The sequence back is from the fertile ovulatory cycle, through the deficient or short luteal phase, LUF, anovulatory ovarian activity to no ovarian activity, the rapidity of change being dependent on the severity of the stress and the sensitivity of the woman to stress. Nothing can be predicted, stages may be skipped or reversed at random. These changes are normal responses to the environment and therefore all the types of ovarian activity in the continuum can be considered to be normal. The process was well demonstrated in a study of ovarian activity in elite women rowers carried out by Harvard University (Snow *et al.*, 1989.) where intensity of training was the stress factor. Five oarswomen showed no change in menstrual function throughout the study (group A), and five showed changes (group B). Ovarian function was assessed by twice weekly pregnanediol measurements using GLC (method B) throughout a year divided into three phases of low, high- and low-intensity training. The figure reported by Snow *et al.* (1989) shows a group B oarswoman who registered the characteristic values of the fertile ovulatory cycle initially, these changed to deficient luteal phase, LUF and then anovulatory ovarian activity during the phase of intensive training and returned within months to the characteristics of the fully fertile ovulatory cycle when intensive training ceased. The phenomenon is best explained as being an evolutionary development to ensure that the added demands of pregnancy were avoided during times that were unfavourable for the survival of the mother.

This is the first time that specific pregnanediol values have been assigned to distinguishing between the fertile ovulatory

cycle, deficient luteal phase, LUF and anovulation. The problem with setting criteria is that a fertile ovulatory cycle is defined as one in which a continuing pregnancy can occur. However, when this is tested by pregnancy the pregnancy rapidly alters the hormone values in the period after ovulation during the time that the luteal phase would have occurred. Thus careful monitoring is required during this period to identify a potentially fertile or infertile cycle. The Day 21 blood progesterone test is completely inadequate for this purpose. In establishing our criteria for diagnosing luteal phase deficiency, it is necessary first to have an accurate reference point. In the present survey the ovulatory oestrogen peak was used which itself may be in doubt by one day when a composite peak is present. This requires daily monitoring. The next requirement is to monitor progesterone production for the next 6 days before a pregnancy starts boosting luteal function. Our definitions are based on two observations. The first is derived from inspection of more than 50 natural conception cycles where pregnanediol excretion was measured daily for the first 6 days after the ovulatory oestrogen peak. There was no exception to the rule that the pregnanediol values should exceed a value of 3 mg/24 h (13.5μM/24 h) for at least 1 day and preferably 2 or more days by Day 6. The second criterion is derived from the rule that a good luteal phase requires first a good follicular phase (DiZerega and Hodgen, 1981). The finding of luteal phase pregnanediol values which do not reach 3–3.2 mg/24 h (13.5–14.4 μM/24 h) in a woman presenting with infertility is good reason for enhancing the hormone values with clomiphene therapy. This greatly increases the chances of pregnancy (unpublished data). That the luteal phase should last for 11 days or more after the ovulatory oestrogen peak and that a length of 10 days or less defines a short luteal phase is now generally agreed to within a day (Smith *et al*., 1984).

The deficient luteal phase based on these criteria is, in our experience, the most common cause of infertility. It has been encountered in every population of ‘normal’ women and in one, reached one-third of the total cycles. This phenomenon was also debated by Johansson *et al*. (1971). This frequency is not unexpected because it is the first step in a regression from the fertile ovulatory cycle and more severe stress and more sensitivity to stress are required to produce the more severe forms of infertile activity. Importantly, the finding of a deficient luteal phase in one cycle of an individual does not mean that the next cycle will also be deficient—the condition is sporadic and unpredictable. It is the main reason why ovulation does not necessarily confer fertility.

Hormone profiles and bleeding patterns in the various cycle types

Hormone profiles and some bleeding patterns are included in Figs. 1–9. The uterine bleeding that occurs in ovulatory cycles is the result of withdrawal of progesterone produced by the corpus luteum that has acted on an oestrogen primed endometrium to produce a secretory endometrium. The bleeding occurs 11–17 days after ovulation, is usually controlled in amount and is termed ‘normal menstruation’. This bleeding always follows ovulation provided the woman is not pregnant or no abnormality exists.

Hormone values and fertility and infertility

Firstly, fertility is associated with marked daily changes in hormone output. Any pattern that shows no changes from day to day denotes infertility. This has recently been reported by Kol and Homburg (2008) but it has been applied by the Billings' method of NFP for 40 years. Secondly, achievement of pregnancy in the current cycle is proof that the cycle is fertile. The next best proof of ovulation is provided by the post-ovulatory rise in progesterone production following an oestrogen peak and fall. In the Billings' Method this is shown by a build-up in cervical mucus production followed by a sudden change to minimal mucus (the Peak symptom). This change is caused by the post-ovulatory rise in progesterone output and its anti-estrogenic effect on the cervix. Thirdly, we have never documented more than one ovulation during a cycle. When multiple ovulations occur they do so over a very short time interval when two or more follicles are exactly synchronized (Brown, 1978). Fourthly, when ovulation occurs it is always followed after an interval by bleeding whether the luteal phase is normal, short or deficient, provided the woman is not pregnant and no abnormality exists. Fifthly, the fertile ovulatory cycle with an adequate luteal phase is the only type of ovarian activity that can produce a continuing pregnancy.

References

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