

## Ovarian Activity and Fertility and the Billings Ovulation Method

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### Ovarian Activity and Fertility

Ovulation - the release of an ovum by the ovary and therefore the only time during the cycle when the ovum is exposed for fertilization--is the central event of the fertile ovarian cycle. It determines the time when pregnancy can occur from an act of intercourse which is the period of 3-4 days (rarely 5-6 days depending on the cervical mucus) before ovulation determined by the fertilizing life span of the sperm and up to 24 hours after ovulation determined by the fertilizable life span of the ovum. Outside this time period a woman cannot conceive from an act of intercourse no matter how hard she tries. Even within this time period, pregnancy from an act of intercourse is not a certainty, the chances vary depending on the couple and the timing of intercourse in relation to ovulation. Maximum fertility is reached during the period of 24 hours before ovulation and several hours afterwards. If the chances of pregnancy at this time are 70% per cycle, it takes two cycles for 90% of couples having intercourse on the most fertile day to achieve pregnancy. If the chances at the beginning of the fertile period are 10% per cycle, it takes 24 cycles for 90% of couples having intercourse at this time to achieve pregnancy. Many authorities would say that the chances are much less than the figures given. Even with in vitro fertilization (IVF), which many would like to think is the ultimate in assisted pregnancy, most health funds allow up to six cycles of treatment. Thus, couples who break the rules of the Billings Ovulation Method (BOM) and do not become pregnant should not conclude that the rules do not apply to them, chance has been on their side. Alternatively, if they have had intercourse on the most fertile day they should not expect pregnancy to follow as a certainty. In animals, Nature has ensured a maximum fertilization rate (but not 100%) by restricting intercourse to the most fertile day of their cycle by the phenomenon of oestrus. Thus the assessment of ovarian activity and the accurate timing of ovulation are basic requirements in natural family planning (NFP) for avoiding pregnancy and under all circumstances including IVF for achieving it.

There are six main methods by which ovarian activity can be monitored and the time of ovulation determined.

#### 1. Vaginal bleeding

Every woman is taught to document her bleeding pattern and this is the method used to assess ovarian activity since the human race began. Onset of vaginal bleeding is used to mark menarche and its cessation marks the menopause. Pregnancy is indicated when regular menstruation stops abruptly. Physiological bleeding is the result of shedding of the lining of the body of the uterus (the endometrium) after stimulation by the hormones oestrogen and progesterone produced by the ovaries during ovarian activity. It usually results from withdrawal of oestrogen and progesterone activity at the end of an ovulatory cycle. Such bleeding is called menstruation. Bleeding can also be the result of oestrogen activity alone produced by an ovarian follicle which has not ovulated. This is called anovulatory bleeding.

Bleeding is the end result of the ovarian activity, it gives little information about the ovarian events which have preceded it and it occurs at variable levels of hormone withdrawal. In an ovulatory cycle, the time of ovulation can be calculated as occurring 11-16 days before the onset of the following menstruation. Women with menstrual cycles which are regular enough for the date of menstruation to be predictable can also predict the date of ovulation by this calculation. This is the basis of the rhythm calculations which were used in the earliest methods of NFP. However, no woman is completely regular for the whole of her reproductive life and, even for the most regular women, errors in the calculations eventually occur, particularly during times of stress, lactation and approach of menopause.

## 2. Cervical Mucus and Related Vaginal Discharges

Oestrogen produced by the ovaries during ovarian activity causes production of mucus by the cervix and it also causes growth and shedding of the epithelial cells lining the vagina, the responses depending on the degree of ovarian activity and on the amounts of oestrogen being produced. These two sites are more sensitive to oestrogen action than the endometrium and the changes can be observed even when the ovarian activity and the oestrogen levels produced are insufficient to cause bleeding, such as in the lead up to menarche. These are the sources of the vaginal discharges utilized in assessing fertility and infertility by all of the modern methods of NFP including the BOM. The way the BOM does this is unique. While the woman is in the upright position such as when doing her normal daily activities, the vaginal discharges drain into the vulval areas and are felt as a sensation there which is either dry, sticky or progressing to slippery. The woman is continuously aware of these sensations without deliberately thinking about them or investigating them and, by understanding their significance, is in touch with the underlying ovarian activity and her fertility throughout the day. While the woman is asleep, the discharges do not drain away so that time for the woman to be in the upright position is required for the sensations to be appreciated. When ovarian activity is absent and no oestrogen is being produced there is usually no discharge and the feeling is one of dryness which persists throughout the period of inactivity ("dry basic infertile pattern" or "dry BIP"). Alternatively, a woman may experience a slight unchanging discharge at this time. This BIP is due to small amounts of mucus being shed from the mucus plug in the cervix. When a small amount of ovarian (follicular) activity is present but not progressive, oestrogen is produced in small and constant amounts and this causes a discharge which comes mainly from the vaginal epithelial cells ("BIP discharge"). Greater ovarian activity which still does not progress results in higher constant levels of oestrogen production which cause a small but constant production of mucus by the cervix. This third BIP is usually only seen during breast-feeding and the approach of menopause. Thus the three BIPs are the result of different levels of oestrogen production, the essential feature being that oestrogen production remains constant for a period of time. A change from one oestrogen level to another is recognizable by a change from one discharge to another, but the change and the new discharge do not progress ("do not go anywhere") and thus differ markedly from the changes in the oestrogen levels and the discharges seen during the progressive lead up to ovulation. During a BIP, once it is established that it is a BIP, the Early Day Rules for intercourse are followed.

Before ovulation can occur a follicle containing an egg must commence and complete its rapid growth phase and this causes marked changes in the vaginal discharges. The oestrogen output rises from a base line corresponding to minimal or absent follicular activity and increases during the rapid growth phase at a rate of approximately 1.5 times per day over a period of 5-6 days. This results in an immediate change from a BIP (the "oestrogen rise" or "ER") followed by a rapidly changing mucus pattern. Thus any change in the BIP can herald either the beginning of another BIP associated with another phase of infertility or, more usually, the beginning of the rapid growth phase of a follicle associated with the fertile phase of the cycle and impending ovulation. Therefore, a period of wait-and-see abstinence at this time is required to distinguish between the two possibilities. When a follicle is proceeding to ovulation, the increasing oestrogen production causes important changes in the cervical mucus which are listed elsewhere (mucus with fertile characteristics). The important feature of this mucus is that it is changing daily to more fertile characteristics in line with the rising oestrogen output of the growing follicle, an important final feature being a slippery sensation (lubrication). This progressive mucus symptom marks the fertile phase of the cycle. If the aim is pregnancy avoidance, the identification of the change from the preceding BIP (the ER) provides sufficient time to allow for the longest fertilizing life span of the sperm before the ovum is available for fertilization at ovulation.

The LH surge which initiates ovulation of the developed follicle, also causes the second ovarian hormone, progesterone, to be produced by the follicle. This production is small but significant at first and then increases rapidly after ovulation. This progesterone strongly reverses the action of oestrogen on the cervix and vaginal epithelium and causes the discharges to rapidly lose their fertile characteristics. This change due to progesterone (the "progesterone change" or "PC") is readily recognized. It is a very important symptom because it shows definitely that ovulation is occurring and is closely related in time to ovulation. With this knowledge, the remainder of the ovulatory cycle can be predicted with confidence. The BOM uses the term Peak day for the day of peak fertility and defines it as the last day of mucus with fertile characteristics (slippery) before the PC. The Peak day is not necessarily the day of maximum mucus production and it is not unusual for a woman to notice the slippery sensation in the morning and to follow the PC as it progresses during the day. In this case the Peak day and the PC occur on the same day. Ovulation occurs on the Peak day or the day of the PC, or occasionally on the next day. Thus the PC times ovulation to within  $\pm 24$  hours. The rule of the BOM for calculating the end of the fertile period from the Peak day and entry into the post-ovulatory infertile phase (the Peak rule) allows for the range of this timing and for the fertilizable life span of the ovum. When this post-ovulatory infertile phase has been reached, pregnancy from an act of intercourse is impossible and, for pregnancy avoidance, all days are available for intercourse until the commencement of the next menstruation.

Thus the fertile phase of the cycle (the "window of fertility") can be recognized by beginning with the first change in the discharge from a BIP (the ER) progressing with fertile characteristics in line with the rising oestrogen production. Ovulation can be recognized by the progesterone change (the PC) and the end of the fertile phase can be calculated from this. The letters in the words "prompt day" summarize the events occurring on the day of the PC, i.e. progesterone rise, ovulation and mucus past, today. The BOM adds 3 days after the Peak day to be 100% certain that the post-ovulation infertile days have been reached.

Besides identifying the underlying ovarian activity and timing ovulation, cervical mucus with fertile characteristics is itself important for fertility, being necessary for maintaining the fertilizing capacity of the sperm and for their passage from the vagina through the cervix to the fallopian tubes. As menopause approaches, the ageing cervix may lose its responsiveness to oestrogen so that no mucus is observed even though ovulation is occurring. Such women are infertile. However, in this event, care in observation is required in case a brief discharge of mucus conferring a brief period of fertility is missed. Absent or poor mucus production before ovulation in a woman being investigated for infertility is often the cause of the infertility. It should be remembered that inhibition of cervical mucus production is an important point of action of the contraceptive pill through the progestogen it contains.

## 3. The LH Surge

The surge in LH production by the pituitary gland triggers ovulation which occurs approximately 36 hours after the beginning of the rise in LH or 17 hours after its peak. Thus the time of ovulation can be determined to within a few hours by either criteria. The LH peak day is readily identified using home kits and, as it immediately precedes the day of maximum fertility, it is commonly used for timing intercourse for pregnancy achievement. To detect the beginning of the LH rise requires more sensitive laboratory assays. However, this was the procedure used in IVF for timing egg pickup in unstimulated cycles because it provided an accurate 36-hour period for preparing for the laparoscopy. Today it is usual to hyperstimulate the ovaries to produce multiple follicles and eggs and then ovulation can be induced at a prearranged time by giving the ovulating dose of HCG 36 hours beforehand. Nevertheless, ovulation does not necessarily occur in the ovary following an LH surge from the pituitary, as can be seen from the later section describing the continuum of ovarian activity (see p. 17). Furthermore, ovulation has been documented without an LH surge being identified, although some release of LH must have occurred to trigger the ovulation. The rise in progesterone output to reach a level which can be defined for the majority of women is actually a more reliable marker of ovulation and a better

proof that there has been an LH surge and that the ovary has indeed ovulated in response to it.

#### 4. Basal Body temperature (BBT)

The rise in progesterone output at ovulation which causes the termination of mucus production also causes a rise in basal body temperature of approximately 0.3 degrees Centigrade. This rise is readily measured and has been widely used for confirming that ovulation has occurred. However, the rise in temperature in relation to the changes in progesterone levels is very variable so that the timing of ovulation by the temperature shift can be in error by up to -1 to + 4 days. The information is retrospective and is of no value in predicting ovulation. The Symptothermal methods of NFP include measurement of the BBT to determine that ovulation has occurred and to calculate the beginning of the post-ovulatory infertile phase. The BOM considers that measuring the BBT is unnecessary and that the progesterone change in mucus production (PC) provides all the necessary information.

#### 5. Measurement of Oestrogen and Progesterone Output

By observing the changes in the vaginal discharges the BOM effectively measures the cyclic changes in oestrogen and progesterone output by the ovaries. Oestrogen and progesterone levels can be measured in blood by radioimmunoassay or their metabolites can be measured in urine. Blood assays are widely used but have the disadvantage that the stress of daily sampling, which is necessary to provide the complete picture of ovarian activity around ovulation, can inhibit ovulation. Most of the validation of the BOM has been done using urine assays. Women have no difficulty in collecting urine daily (3 hour collection) and the assays have been simplified to the stage that women themselves can do accurate testing at home (using the Home Ovarian Monitor). This device is used in many BOM centres to help women who need reassurance that they are interpreting their symptoms correctly and it has many applications in assisted reproduction and in further research.

#### 6. Ultrasound Scanning

The growth of follicles, rupture of a follicle (ovulation) and development of a corpus luteum can be visualized by ultrasound scanning. In fact, the actual rupture of the follicle, the extrusion of the ovum and follicular fluid, the blood supply to these structures and the degree of stimulation of the uterine endometrium as a result of the hormones produced, can all be readily seen. This is thus the most accurate method of timing ovulation. Ultrasound scanning has played an important role in providing basic information on all phases of ovarian activity, and its agreement with the findings based on the hormone patterns and mucus symptoms has added much to the confidence we have in the rules of the BOM. For daily application, ultrasound scanning is expensive and therefore it is usual to assess ovarian activity by another method and use ultrasound scanning as the final confirmation that ovulation is imminent.

### Physiology of Ovulation

Ovulation occurs over a period of about 15 minutes and even when more than one ovum is released, as in a twin pregnancy, the multiple ovulations occur very close together in time. Thus ovulation is the one event in the menstrual cycle with a very precise time frame. The ovulatory mechanism produces the two ovarian hormones, oestradiol and progesterone. The ovum is contained within an ovarian follicle and matures as the follicle goes through its rapid growth phase. During this rapid growth phase the follicle produces increasing amounts of oestradiol. This oestradiol stimulates the glands of the cervix to secrete a particular type of mucus ("mucus with fertile characteristics") which is essential for the sperm to pass through the cervix to reach the ovum. Oestradiol also stimulates growth of the endometrium which lines the body of the uterus, i.e. the womb ("proliferative phase"). After rupture of the follicle and release of the ovum, both progesterone and oestradiol are secreted by the corpus luteum which forms from the ruptured follicle. The rapid rise in progesterone secretion strongly counteracts the effect of oestrogen on the cervix and vaginal epithelium and thus causes the progesterone change (PC) in the mucus pattern which occurs near ovulation and defines the Peak day (the last day of mucus with fertile characteristics before the change). Progesterone also acts on the oestrogen-primed endometrium making it suitable for implantation of the fertilized ovum ("secretory phase"). In the absence of pregnancy, secretion of oestradiol and progesterone reaches a maximum approximately 7 days after ovulation and then declines. This leads to shedding of the endometrium as menstrual bleeding 11-16 days after ovulation.

The cyclical changes in ovarian activity are controlled by the secretion of two hormones by the pituitary gland situated in the brain, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Production of these two hormones is controlled in turn by an area of the brain called the hypothalamus. The hypothalamus acts as a computer, analysing nervous signals from other areas of the brain including those generated by the emotions and by environmental factors, such as stress and nutrition; it also analyses hormonal signals (oestradiol and progesterone) generated by the ovaries and other endocrine glands and transmitted by the blood stream. The sum total of these effects determines the quality of the ovarian activity produced.

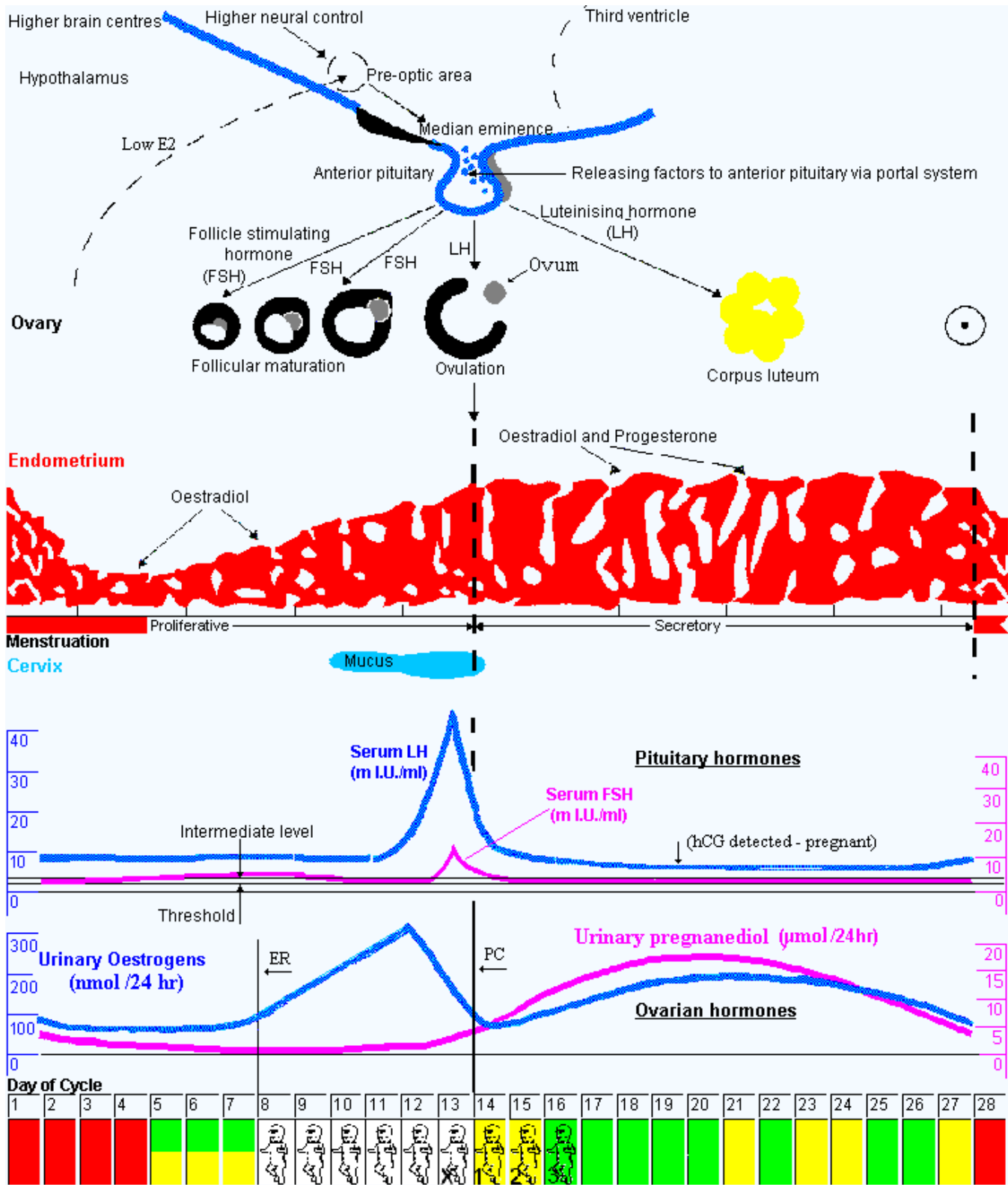


Figure 1. Relationship of the hormonal events of a woman's reproductive cycle to the stamp record. In the pre-ovulatory infertile phase in a cycle of average length the woman will observe dryness (green) or an unchanging discharge (yellow). In an extended pre-ovulatory phase either of the two infertile patterns may occur at different times. ER, oestrogen rise. PC, progesterone change. X (on stamp) = Peak day.

The ovulatory cycle proceeds in a well-ordered series of events (see Figure 1). During the latter half of the preceding cycle, the high output of oestradiol and progesterone by the corpus luteum acting via the hypothalamus suppresses the production of FSH and LH by the pituitary gland. The waning production of oestradiol and progesterone at the end of the cycle removes this suppression and the FSH levels begin to rise. The follicles within the ovaries have a threshold requirement for FSH below which all remain dormant. Initially, the amounts of FSH reaching the follicles are suppressed below this threshold but as the suppression is removed the FSH levels rise and reach the threshold for a few of the most sensitive follicles which include those with the best blood supply. These follicles begin their rapid growth phase while the remaining follicles whose thresholds have not been reached remain in the dormant state. This is an essential mechanism for conserving follicles so that the initial store at birth lasts for the reproductive life span of the individual. This is the recruitment phase of the ovarian cycle. Once a follicle begins its rapid growth phase it has only two outcomes. Either it progresses to its ultimate destiny, ovulation and the potential production of a new individual, or it fails in the race to ovulation and dies in the process of atresia. It cannot return to the original follicle pool. Several days of growth

are required before the growing follicles secrete sufficient oestradiol into the blood stream to provide the signal to the hypothalamus/pituitary that their threshold for FSH has been reached. There is also an intermediate level of FSH production which must be exceeded before a follicle is finally boosted into its full ovulatory response, and a maximum level which must not be exceeded otherwise too many follicles are caused to develop and multiple ovulations occur. The maximum level is only 20-30% above the initial threshold so that the FSH must rise slowly and precise feedback control by the oestrogen produced by the developing follicles is essential.

Selection of the follicle which will ovulate is achieved by the following process. As a follicle develops, its content of granulosa cells increases and it produces rapidly increasing amounts of oestradiol and at the same time its requirements for FSH to maintain its rapid growth diminishes, that is, its threshold for FSH decreases. Thus the most advanced follicle quickly gains the advantage in that it becomes the major producer of oestradiol and this reduces FSH production by the pituitary at a rate sufficient to maintain its own rapid growth but the levels drop below the thresholds of its less advanced competitors so that they stop growing and atresia (die). Only when two or more follicles are exactly equally matched in the race to ovulation do multiple ovulations occur. The fall in FSH levels caused by the rising oestradiol output also turns on a maturing mechanism within the dominant follicle which makes it receptive to the second pituitary gonadotrophin, LH, while its competitors have not reached this stage.

The high oestradiol levels also activate a positive feedback mechanism in the hypothalamus which causes the pituitary to release a massive surge of LH. This surge of LH is the trigger which initiates the ovulatory process and rupture of the follicle (ovulation) occurs approximately 36 hours after the beginning of the surge or 17 hours after its peak. Ovarian production of oestradiol reaches a peak (the pre-ovulatory oestrogen peak) approximately 36 hours before ovulation and then falls as the ovulatory mechanism progresses. This fall is an important marker because it signals the end of the rapid growth phase of that follicle, whether it is proceeding to ovulation or atresia. The LH surge causes some luteinization of the follicle before rupture and this leads to the beginning of progesterone production. Thus a woman monitoring her oestrogen and progesterone output sees a marked rise in oestrogen production to reach a peak followed by a fall. She knows that ovulation will occur within 24 hours after identifying the day of the fall and that this is the most fertile day of her cycle. If ovulation is actually occurring, i.e. the LH surge has occurred and has triggered the ovulatory process, she also sees on the day of the fall a small rise in progesterone output. The actual level of progesterone output associated with the moment of ovulation can be specified within a small range which applies to most women, and this, in the presence of an oestrogen fall, is a very accurate marker for timing ovulation. However, if the fall happens to signal the end of the rapid growth phase of a follicle which is not going to ovulate, no rise in progesterone is seen (anovulatory cycle) or a small rise is seen which is not progressive (luteinized unruptured follicle). After ovulation, the ruptured follicle is transformed into the corpus luteum and production of progesterone increases rapidly (approximately doubling each day) together with a second rise in oestradiol output. The rise in progesterone levels causes the progesterone change in the cervical mucus which allows the Peak day to be calculated. The decrease in the progesterone levels towards the end of the cycle causes the bleeding - menstruation. Oestradiol output also falls at the end of the cycle but this fall is less important in inducing bleeding than the fall in progesterone output. Bleeding always follows the post-ovulatory rise and fall in progesterone output but a corresponding rise and fall in oestradiol output without the production of progesterone, as in anovulatory ovarian activity, may or may not be followed by bleeding.

## Cycle Variants : the Continuum

The time taken for the total fertile ovulatory process, that is, the beginning of the rapid growth phase of a follicle, its development, ovulation, formation of the corpus luteum and its demise (at menstruation), is always approximately 21 days. In a 28-day cycle it takes about 7 days for the FSH values to rise to threshold and for a follicle to commence its rapid growth phase. During these 7 days very little oestradiol is produced and the woman experiences several days of a BIP after cessation of bleeding. Many variants of the 28-day ovulatory cycle may occur. Fully ovulatory cycles as short as 19 days have been observed. In these the oestrogen values were already rising on day 1 of the cycle showing that a follicle was developing at this time and the fertile phase had begun. Alternatively, the rise in FSH production to the threshold may be delayed and this is one of the causes of lengthening of the cycle. While the FSH levels remain below the threshold no follicle begins its rapid growth phase, very little oestradiol is produced, and the cervix remains unstimulated. The woman experiences an unchanging succession of "dry" days or days with minimum vaginal discharge (BIP). However, unless the woman has reached the menopause or has permanent amenorrhoea, the FSH output eventually rises above the threshold and the ovulatory events are set in train with the same timing as in the 28-day cycle.

In another variant, the FSH levels rise to exceed the threshold, a follicle develops but does not progress to ovulation. The developing follicle produces oestradiol causing a corresponding change in the vaginal discharge. The FSH levels may then return to sub-threshold values, the follicle atreses, the oestradiol levels return to their baseline values with a return to the dry BIP. No LH is released, no progesterone is produced and no PC day or Peak day is identified. Depending on the amount of oestradiol produced and the sensitivity of the uterine endometrium of the individual, there may or may not be sufficient stimulation of the endometrium to result in an oestrogen withdrawal bleed. If bleeding does occur, this is anovulatory bleeding (see below). The next follicle which develops may have the same fate but eventually a follicle develops and proceeds to a full ovulatory response. In this case, the woman sees patches of mucus production when each follicle is partly developed and the oestradiol levels are correspondingly elevated with intervening return of the BIP when the follicle atreses and the oestradiol levels return to base line. However, when the follicle that eventually ovulates develops, mucus production then shows progressive development, and a progesterone change and a Peak day are recognized. Thus the woman can conclude that she has ovulated, she can calculate her entry into the post-ovulatory infertile phase and predict that menstruation will occur approximately 14 days later. Such transient attempts at follicular development before full follicular maturation and ovulation constitute another cause of long cycles.

In yet another variant, the rise in FSH production above the threshold may arrest before the intermediate level is exceeded and the follicles remain in a state of chronic stimulation. The amounts of oestradiol secreted stabilize at levels less than those of the pre-ovulatory peak. The vaginal discharge shows fertile characteristics corresponding to the oestradiol levels reached but these do not progress. If this situation persists the stimulated uterine endometrium may break down as oestrogen breakthrough bleeding. The FSH levels may then return to sub-threshold levels, the oestradiol levels return to base line and the vaginal discharge returns to the dry BIP. However, more usually, the feed-back mechanism corrects itself, the FSH values begin to rise again, they exceed the intermediate threshold and a follicle is boosted to ovulation with the same mechanisms, timings and Peak day calculation as in the 28-day ovulatory cycle. This situation is the cause of pre-ovulatory bleeding or spotting. Indeed, it is the final rapid rise in oestradiol output to the pre-ovulatory peak which stops the bleeding and the woman should be aware that she is in a phase of high fertility during such a bleed, i.e. a bleed which has not been preceded approximately 14 days earlier by an identifiable progesterone mucus change (PC).

In other variants of the ovarian cycle a follicle is boosted towards ovulation but the release of LH is faulty. Sometimes the release mechanism may not operate at all, there is no LH surge resulting from the raised oestradiol levels, the boosted follicle has a limited life span, it atreses and the resulting fall in oestradiol output signalling the end of the follicle's rapid growth phase results in oestrogen withdrawal bleeding. The raised oestradiol levels cause mucus to be produced but no PC day (or Peak day) can be identified because there is no rise in progesterone production. This is one form of anovulatory ovarian activity. In another form, some LH is released but not in sufficient amount to cause rupture

(ovulation) of the boosted follicle but sufficient to cause a small amount of luteinization of the follicle which in turn causes a small amount of progesterone to be produced for a short period of time. This is known as the luteinized unruptured follicle (LUF). No clear PC day (or Peak day) can be identified (the symptoms are "fuzzy"). An LUF may or may not be followed by a bleed and, as in the previous variant, the next episode of ovarian activity may be a fully fertile ovulatory cycle or a repeat of a variant.

Another variation is seen when the LH surge is sufficient to cause ovulation but is insufficient to produce a fully formed corpus luteum capable of supporting a pregnancy. The progesterone levels rise above those seen in an LUF, usually sufficient to cause a PC. However, either they do not reach the levels seen in a fully formed corpus luteum, or they reach normal post-ovulatory values and fall prematurely so that bleeding occurs 10 days or less after ovulation. The first is known as the "deficient luteal phase" and the second as the "short luteal phase". Both cycles are ovulatory but infertile, both are followed by menstruation and the Peak rule applies. The deficient luteal phase may be associated with some difficulty in recognizing a PC and calculating the Peak day or of diagnosis by hormone assays, and the short luteal phase can be recognized by the shortened interval between the Peak day and menstruation. A cycle which results in a continuing pregnancy must ipso facto be a normal fertile cycle. However, when the luteal phase progesterone levels of such a cycle are in the lower range of normal it is difficult to distinguish that cycle from an infertile cycle with a deficient luteal phase. The distinction is unimportant for pregnancy avoidance but it is important for pregnancy achievement where persistently low luteal phase progesterone levels can be enhanced by giving clomiphene and this is an important means of increasing pregnancy rates in these cases.

These cycle variants have been described as if they were separate entities. Actually, one merges into the next so that there is a continuous gradation from no follicular activity (amenorrhoea) through follicular activity without an LH surge (anovulatory ovarian activity), through increasing maturation of the LH mechanism up to the fully fertile ovulatory cycle. We term this the "continuum" of ovarian activity. At menarche, the first bleeding cycle is usually anovulatory and it may take several years for the full LH response to mature and fertile ovulatory cycles to commence. The reverse occurs as menopause approaches. Return of fertility after childbirth and during breast-feeding is similar to the mechanism at menarche but the time intervals between the variants are shorter. In athletes, a woman with regular ovulatory cycles frequently shows changes during times of intensive training, first to deficient luteal phases, then to LUFs, anovulation and finally amenorrhoea and then reverts back within a few months of ceasing training to fully fertile ovulatory cycles. The cycle variants do not necessarily repeat themselves from cycle to cycle. For example, with approach of menopause or during stress, the woman may experience periods of amenorrhoea or a series of anovulatory cycles or LUFs interspersed with fully fertile ovulatory cycles. As pregnancy can result from only the fully developed ovulatory cycle, one would expect that all the days that the other cycle variants were in progress would be available for intercourse if the aim is pregnancy avoidance. The problem is that the build-up to these infertile cycle variants is the same as for the ovulatory cycle and the fact that they were actually infertile is seen only in retrospect by the absence of a distinct PC or a shortening of the luteal phase. Thus vigilance is required at all times and the Early Day Rules of the BOM are applied until a distinct PC is felt. The cycle variants should not be considered as abnormal, they are normal responses to the environment to ensure that pregnancy does not occur under very unfavourable conditions for the mother and fetus. Being able to identify an infertile cycle variant while it is still in progress is the aim of future research.

## The Rules of the Billings Ovulation Method

### Early Day Rules for Pregnancy Avoidance

For pregnancy avoidance the BOM has four rules, three Early Day Rules and the Peak rule. The Early Day Rules are formulated to give the earliest possible prediction of ovulation to allow for the longest possible sperm survivals. As the BOM relies on sensation at the vulva, and time is required for the discharges to drain into the vulval area, time by the woman in the upright position is required for accurate identification. Furthermore, seminal fluid obscures the observations and needs to be absorbed or drained away before accurate observations can be made. Therefore, to achieve these two requirements for all the types of ovarian activity the Early Day Rules state the following:

1. Times of the full menstrual flow or other types of bleeding are not available for intercourse since these obscure the discharge symptoms. Intercourse may be resumed towards the end of menstrual bleeding (that is bleeding following a distinct PC and Peak day) when it is light or spotting is occurring, provided that the fertility symptoms are not being obscured.
2. When a BIP is identified, alternate evenings are available for intercourse.
3. When a change from a BIP discharge or bleeding is observed the couple waits without intercourse. If the same BIP returns, intercourse may be resumed on the fourth evening after the return of the BIP. This is the wait and see, one, two, three rule.

More usually, the change from a BIP is progressive with the discharge changing daily in characteristics which are becoming increasingly fertile, slipperiness being the most important final quality. The phase of possible fertility begins with the first change from the BIP (the ER) and from then on a time of no genital contact is observed. In short cycles, there may be insufficient time after bleeding to identify a BIP before a follicle begins to develop, in which case no pre-ovulatory days are available for intercourse. Occasionally during breast-feeding or approach of menopause, a BIP may change to another BIP with more fertile characteristics. In this case a wait-and-see period of 2 weeks is required before assuming that the change is in fact to a new BIP before resuming intercourse. The woman notes that the change is not progressive ("not going anywhere"). When no PC providing recognition of the Peak day is observed, the woman continues to apply the Early Day Rules.

### The Peak Rule for Pregnancy Avoidance

The Peak day is the last day that mucus with fertile characteristics (slippery) is felt before the progesterone change (PC). It is thus determined retrospectively by this change. The Peak rule states that intercourse may be resumed on the fourth morning after the Peak day. All times from then until the next menstruation are available for intercourse. The Peak rule provides a well-tested minimum safety margin between the resumption of intercourse at the beginning of the post-ovulatory infertile phase and the Peak day, which is the day of maximum fertility.

### Pregnancy Achievement

For pregnancy achievement, the couple aims to have intercourse on the Peak day, the day of peak fertility. However, the Peak day is identified in retrospect by the progesterone change, and, furthermore, intercourse on the Peak day produces seminal fluid which obscures this change. Therefore, in these circumstances, the Peak day cannot be determined with certainty. The best that can be done is to have intercourse when the discharges seem to be maximally fertile, namely when a slippery sensation is felt at the vulva. This is understood more clearly by those women who have had previous experience with their symptoms in avoiding pregnancy. When the timing is correct and no pregnancy results, the couple

usually begin to despair and want to know the reason. Fertility is one of the most variable phenomena in human activity and is the sum total of both partners' fertility. The most fertile couples are those where the man produces the most robust and numerous sperm and the woman provides the longest and best cervical mucus production to nurture them. Such couples conceive following almost any act of intercourse during the fertile phase with a pregnancy rate of about 70% per act of intercourse during the fertile phase. At the other end of the spectrum, the combined sperm/mucus interaction of the couple may be so poor that the sperm have fertilizing ability only for the few hours of optimum mucus production close to ovulation. These couples are self selecting and are the main group presenting with infertility. They have a probability of conception of about 10% per cycle and therefore, without accurate timing of intercourse, it would take several years of trying before the majority had achieved pregnancy. When conception has not occurred within say six successfully timed cycles using the BOM symptoms, it is worth trying even more accurate methods of timing ovulation such as the LH kits or the Home Ovarian Monitor. Failing to conceive when wanted is stressful and therefore favours infertility. It should be remembered that, apart from a few conditions such as blocked fallopian tubes, absent sperm and continued anovulation, most couples will conceive eventually without help. However, the modern expectation is one of immediate results and the main function of assisted reproduction techniques is therefore to shorten the waiting time for conception.

It is seen that the rules of the BOM cope effectively with all the types of ovarian activity yet discovered. It should be emphasized that the BOM recognizes only one type of cycle, that is the ovulatory cycle in which a PC providing calculation of a Peak day is observed and which therefore ends with menstruation. This includes the fully fertile ovulatory cycle and the infertile ovulatory cycles with deficient or short luteal phases. The first day of menstruation is counted as the first day of the cycle. Bleeding which occurs without a Peak day preceding it is not counted as the end of a cycle but is considered to be still the early part of an ovulatory (possibly fertile) cycle which will follow it. Thus the emphasis in the BOM is on cyclic fertility. This contrasts with other definitions which refer to cycles of bleeding or cycles of ovarian activity. Thus it is possible to have ovulatory or anovulatory cycles of bleeding or of ovarian activity. In our work in measuring hormone production the term "cycle" has been applied to the growth and regression of follicles within the ovaries whether they ovulate or not by measuring the rise and fall in oestrogen and progesterone production. Thus this application of the term "cycle" refers to cyclic ovarian activity which is related to but not identical with cyclic fertility. The distinction is made by the BOM to steer women away from the old concept of concentrating on the bleeding symptom, which is uninformative, and making them concentrate on the fertility symptoms which are really what matter. Furthermore, the BOM concentrates on the patterns of discharges which reflect the underlying dynamic ovarian events associated with fertility and infertility rather than on the detailed descriptions of the discharges which vary from woman to woman.

## Research Effort

The BOM was developed only after a complete appraisal of the NFP methods which were available in the late 1950s, including the rhythm method and the use of the BBT, and finding that none could hope to match the newly developed contraceptive pill in efficacy and acceptability. The above understanding of the application of the vaginal discharge symptoms to fertility awareness, as applied in the BOM, has been arrived at after more than 30 years of intensive research which has had little support from granting bodies. Firstly, the observations were made on the women themselves as the rules were developed and used in practice. Some women planning pregnancy volunteered to test their fertility on days relative to the Peak day and all pregnancies were carefully assessed as to the timing of the intercourse which caused them. Secondly, Professor Erik Odeblad, in Sweden, has done years of pioneering work on typing the cervical mucus and determining the significance of each type in the fertility process. Thirdly, the above study of the relationship between the mucus changes, ovarian activity and fertility involved approximately 750,000 hormone assays for both pregnancy avoidance and achievement, countless ultrasound observations and the monitored use of FSH, LH (HCG) and clomiphene in the induction of ovulation. Such a large study has been necessary because approximately 90% of ovarian cycles are ovulatory and the remaining 10% are distributed among the other variants. The ovulatory cycle has been extensively studied by many workers but the other variants have been largely overlooked. This is because these other variants are not predictable and large numbers of cycles needed to be studied so that the variants could be documented and their mechanism, frequency and impact on the mucus symptoms and fertility determined. To expedite the study, the search was concentrated on those times when these cycle variants are most common, namely menarche, stress, infertility, postpartum, breast-feeding and approach of menopause. Because NFP operates with an intact and functioning reproductive system, it has been important to study all the types of ovarian activity that occur in women so that the times of possible fertility and absolute infertility can be recognized with certainty and the full potential of the method can be realized. The work involved in the overall development of modern methods of NFP has necessarily been far more extensive and demanding than that required for other methods of family planning, all of which are designed to interfere predictably in the intricate processes of reproduction and the main research requirement has been to determine efficacy, acceptability and the minimization of deleterious side effects. It should be stated that much of this research in NFP has been conducted in parallel with research in assisted reproduction and that each field has made important contributions to the other. In fact, it is unlikely that the full potential of either field is possible without the information provided by the other. This is the direction of further research.

## About the Author

This section is written to support the authenticity of the studies reported here and to show that they are part of the mainstream of research in human reproduction. Historically, mainstream research in reproduction and its publication have been dominated by the aim of halting the world population explosion and more recently by the expectation that the main aim of the research is to make profits. Natural family planning (NFP) has not been seen to fit in with either expectation and thus funding for research and the ability to publish the findings have not been in proportion to the importance of the research. Furthermore, drug companies are important providers of funds. James Brown has had his share of grants and, in addition, has been fortunate in being able to earn through his laboratory enough to fund the other projects which he has thought important. Also, as he has made the advances, the routine applications have usually been taken over by others and this has freed him to move on to new challenges. Application of the mucus symptom is the one exception. This has been resolutely rejected by his clinical colleagues, the reason being a complete mystery. He believes that achieving the full potential of NFP is the greatest research challenge in human reproduction today and that the Billings Ovulation Method is the nearest to achieving this aim.

James Brown's interest in reproduction began in the 1940s in New Zealand when he observed the rapid progress being made in animal reproduction at the time. This progress was made possible by understanding the phenomenon of oestrus which enabled the fertile time of the animal ovarian cycle and ovulation to be determined with precision (oestrus causes the female to accept the male only at the most fertile time of the cycle). He reasoned that an equally accurate method for timing ovulation in the human would allow the same progress to be made. Furthermore, as Nature uses the interaction between oestrogen and progesterone produced by the ovaries to manifest oestrus, measurement of these hormones was the most likely method of achieving his aim. Consequently he joined the research team in Edinburgh of Professor Guy Marrian who was one of the men who isolated and characterized the oestrogens. During the 1950s the team was successful in developing methods for accurately measuring the metabolites of the oestrogens, progesterone and luteinizing hormone in urine and, for the first time, documented the precise patterns of these hormones throughout the fertile ovulatory cycle and related these patterns to ovulation and fertility.

Having established a reputation in the field, James Brown has been involved in practically every major development in human reproduction since then until his retirement in 1985. He was a member of Dr Gregory Pincus's think-tank for the development of the oral contraceptive pill and performed the early work on its action. He was surprised that the pill was so quickly and universally adopted by women without an adequate study of its safety and possible long-term effects. At the same time he was pioneering work on assisted reproduction including the use of timed intercourse (as used by Nature in the phenomenon of oestrus) and clomiphene and human gonatrophin for women with deficient ovarian activity. The Swedes won the race to be the first to use human gonadotrophin but reported a startling multiple pregnancy and hyperstimulation rate.

In 1962 James Brown joined the Department of Obstetrics and Gynaecology, University of Melbourne. With colleagues, he developed methods for the safe use of human gonadotrophin with the minimum of multiple pregnancies, and for a time produced all the gonadotrophin for clinical use in Australia, New Zealand, Singapore and parts of Canada. From the clinical results, he developed the incremental system of gonadotrophin therapy and propounded the threshold hypothesis of gonadotrophin action on the ovary. The threshold hypothesis explained, for the first time, how only one follicle is usually selected for ovulation in the human, but it took 20 years for the explanation to be universally accepted. The pregnancy rate achieved with gonadotrophin therapy has not been bettered. The key to this success was in mimicking the hormone patterns of the natural cycle as closely as possible, a point which is still not fully appreciated today. He has continually improved the sensitivity, speed and convenience of the methods for measuring oestrogen and progesterone metabolites in urine, so that the lowest concentrations found in the human can be measured. In the early 1970s, the rest of the world changed to blood assays for monitoring ovarian and pituitary activity. The validation of these blood assays depended on demonstrating that the hormone patterns obtained were the same as those obtained by the urinary assays.

With infertility due to anovulation now fully treatable, James Brown joined Professor Carl Wood's team which was developing in vitro fertilization (IVF) for achieving pregnancy in women with occluded fallopian tubes. During the next 7 years he provided the expertise for timing egg pick-up for IVF and also was the optimist that success would ultimately come. His methods for timing egg pick-up were also used for achieving the first IVF pregnancy in Britain. Although he is one of the "fathers" of IVF in Melbourne, he is critical of some of the bizarre applications of IVF, of some of its subsequent developments and its low pregnancy rates.

Other interests include research on hormone-dependent cancers, notably cancers of the breast, endometrium and ovaries. As much time has been devoted to cancer research as to reproduction. Studies were conducted during the 1950s on the effect of endocrine ablation as a treatment for breast cancer. Later, with colleagues at Harvard University, a large international study was conducted on risk factors in the development of breast cancer. This work was awarded the Prix Antoine Lacassagne from Paris in 1986 as the most important contribution to the study of breast cancer for that year.

James Brown met Doctors John and Evelyn Billings in 1962 and immediately appreciated the rightness of their findings and aims. The research that followed and the way it fitted in with his other studies is described in this booklet. As blood is not suitable for the serial assays required for long-term monitoring of ovarian activity, particularly at home, and his laboratory was apparently the only one in the world which was able to perform the urinary assays, he has spent his latter years developing the Home Ovarian Monitor. This system utilizes urine, it is simple enough for women to measure their hormone production at home, it can be used by assisted reproduction clinics to maintain daily control of their treatments and anyone can use it to check the statements made in this monograph. As a final note, the quest for the equivalent of the phenomenon of oestrus in the human is now ended; it is contained in the concepts of the Basic Infertile Pattern (BIP), the oestrogen rise (ER) and the progesterone change (PC) which have come from the work of John and Lyn Billings.

### **Some Recognition for this Work**

1952 Ph.D. Edinburgh; 1958 American Cancer Society Fellowship; 1961 Lecture, Laurentian Hormone Conference, U.S.A.; 1970 D.Sc. Edinburgh; 1971 Professor (personal chair) Department of Obstetrics and Gynaecology, University of Melbourne; 1978 Senior Organon Prize (with Henry Burger); 1981 Fellow, Royal Australian College of Obstetricians and Gynaecologists ad eundem; 1983 Citation Classic, the seventh to be awarded to a worker in Melbourne; 1986 Professor-Emeritus, University of Melbourne, Life Member of the Australian Endocrine Society and of the Fertility Society of Australia.

### **Publications**

Approximately 230 publications in refereed scientific journals and chapters in books.