The "Continuum" of Ovarian Activity: Hormonal Profiles in James Brown's Studies

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Rome 2023

Thank you for giving me this opportunity to talk to you all today. It is wonderful to be here in Rome and seeing you all in person. I have been asked to speak about the work of the late Professor James Boyden Brown. More specifically the hormone profiles of the Continuum of ovarian activity. For those of you who do not know, Professor Brown was my mentor. I worked in the laboratories that were set up and headed by him at the Royal Women's Hospital in Melbourne Australia.

In the title of his last publication in Human Reproductive Update[1], he says this is a "reinterpretation of his earlier findings". How early did it all begin? I guess it really began in 1947, but his life began in 1919. James Brown was born in New Zealand in 1919. By the age of 21 he had gained his Masters in Chemical Engineering.

After working in the Hospital Pathology department during the Second World War, in 1947 he gained a scholarship to work in Scotland. The Clinical Endocrinology Research Unit was headed by Professor Guy Marian, who was one of the world leaders in oestrogen discovery and research. While working in Edinburgh Jim gained his PhD and published several papers.

Before we go any further and talk about his discoveries, we need to have a basic understanding of the term "Continuum of Ovarian Activity". It is said a woman's fertility begins with her first bleed at menarche and ends with her last bleed at menopause. For most of her life she will have fertile ovulatory cycles.

The studies have shown that the young girl, as she traverses from amenorrhea to fertile ovulatory cycles, may have bleeding that is not menstruation; she may have cycles that are not fertile. There is a continuous gradation from no follicular activity to fertile ovulatory cycles.

The studies have also shown that as a woman approaches menopause there is a decline in fertility before she become amenorrhoeic. Once again it is a continuous gradation but in reverse to the young woman.

During her lifetime the woman may have one, two or three children. After the birth of these babies, especially if she is breastfeeding, then once again as she traverses from lactational amenorrhea to fertile ovulatory cycles, she may have bleeding that is not menstruation and cycles that are not fertile.

During her life she may experience stress – perhaps during exam time or as she approaches her wedding day. Maybe it is later in life – perhaps when she has sick and aging parents or maybe due to teenage children. Stress can have an effect on the cycle causing infertility for a short time.

The winding up or winding down of fertility is a normal progression during the woman's reproductive life and is the basic concept of the Continuum of Ovarian Activity.

How was Jim Brown able to develop the concept of the Continuum?

He was part of the team that developed methods for measuring firstly the oestrogens, then pregnanediol and finally gonadotrophins in urine.

1955 was a very important year. Jim published 3 important publications.

1. J.B.Brown - *A Chemical Method for the Determination of Oestriol, Oestrone and Oestradiol in Human Urine*. Biochem J 1955; 60:185-193

2. Klopper AI, Michie EA, Brown JB – *A method for the determination of urinary pregnanediol*. J Endocrinology 1955; 12:209-219

3. J.B.Brown – *Urinary Excretion of Œestrogens during the Menstrual Cycle*. The Lancet: Feb 12, 1955: 320-323

The first paper described the method that Jim and colleagues developed for the quantitative measurement of the 3 different types of oestrogen in urine. The second described the method for the quantitative measurement of pregnanediol. These are important studies as they were both quantitative and both in non-pregnant women.

The third paper was looking at the urinary oestrogens in the normal menstrual cycle.

All of these were ground-breaking – launching Jim Brown as one of the leaders in his field.

Let's take a closer look at the last paper from 1955.

Eight women collected daily 24 hour urine samples throughout the whole menstrual cycle. Two women collected for two cycles. During the study one of the women conceived.

There were some important observations made in this study and these have not changed with more studies and more knowledge.

Firstly – the amounts of oestrogen may vary from woman to woman, but the pattern is the same. For instance, look at the Ovulation peak – oestriol – average is 27 but the range is 13-54, oestrone average is 20 but the range is 11 – 31 and finally oestradiol the average is 9 and the range is 4 – 14. (Figure 1)

ŒSTROGEN LEVELS FOUND AT VARIOUS TIMES DURING THE MENSTRUAL CYCLE
(Collected from ten cycles)

Time in cycle	Œstrogens excreted (µg. per 24 hours)					
	Average			Range		
	Œst-riol	Œst-rone	Œst-radiol	Œst-riol	Œst-rone	Œst-radiol
Onset of menstruation	6	5	7	0–15	4–7	5–9
Ovulation peak ..	27	20	9	13–54	11–31	4–14
Luteal maximum ..	22	14	7	8–72	10–23	4–11

FIGURE 1

The second important point is that the amount of oestrogen is not important but day to day variation is. A single oestrogen test will have little significance, he went on to say, unless it has been collected at an accurately known time in the cycle. (Figure 2)

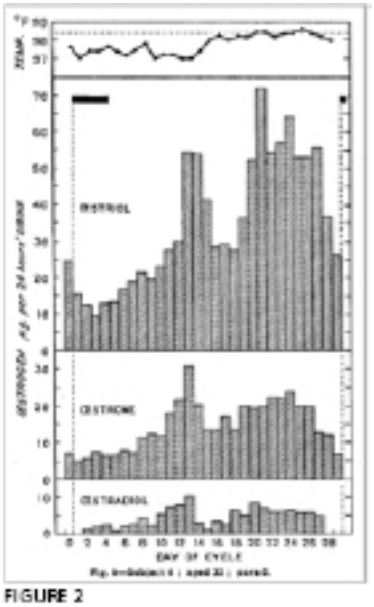


FIGURE 2

It soon became clear to Jim that it was the patterns of oestrogen that were important. Something with which you are very familiar as Billings Ovulation Method® teachers.

The following year Jim published another paper[2] this time following the woman who had conceived in the previous study. Figure 3 shows the preconception cycle and the conception cycle. To us this seems to be normal but to a young Jim Brown this was exciting – this was a first. Both cycles showed the same pattern until the latter part of the luteal phase with oestrogen levels continuing to rise.

This particular woman not only collected throughout the conception cycle but also every day throughout the pregnancy and labour. 3 other women participated in the study although they did not contribute daily samples.

Figure 4 shows the oestrogen levels throughout the pregnancy showing all three oestrogens continuing to rise right up until delivery.

Subject 8 is the generous woman who continued to collect throughout her labour and post-delivery and we

can see the results for the week following parturition. Note the rapid fall.

She continued to collect throughout lactation, until the end of the third menstruation. (Figure 5) There must have been many questions that Jim and colleagues asked themselves. So many times, they must have asked why and how.

The first two bleeds are not menstruation - but why did the woman bleed? In his discussion Jim wrote "slight menstrual bleeding occurred when the oestriol and oestrone levels were each approximately 7µg/24 h".

At this stage there was no understanding of withdrawal or breakthrough bleeding.

Bleed 3 is menstruation – ovulation occurred as we can see a rise in pregnanediol and her Basal Body temperature, but this has a short luteal phase. The next cycle is the same – ovulation with a short luteal phase.

The last cycle has a normal length luteal phase, and the oestrogen levels were almost identical to those during the menstrual cycle preceding pregnancy.

This really is the beginning of the early studies leading to the concept of the Continuum.

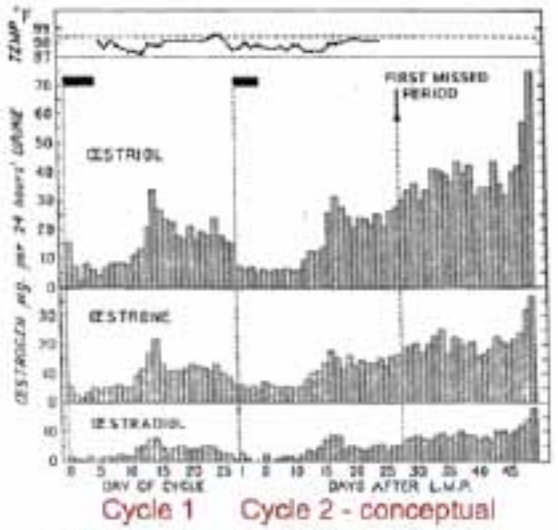


FIGURE 3

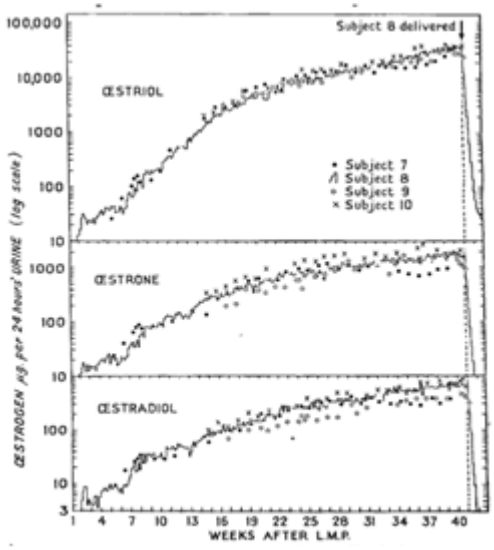


FIGURE 4

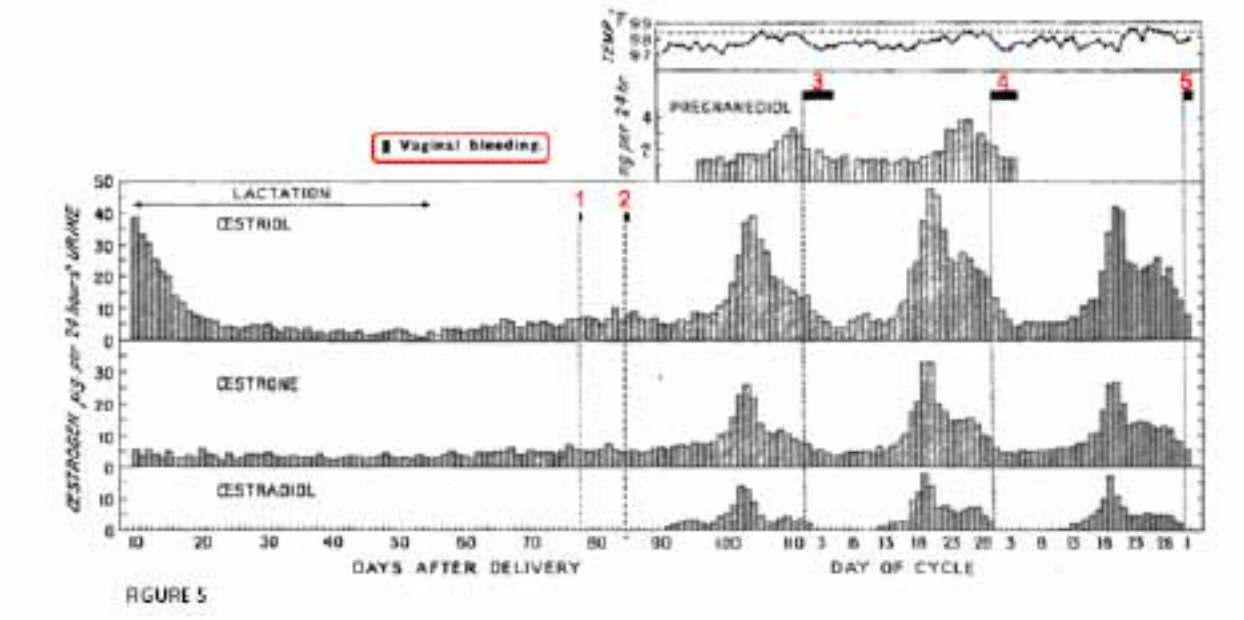


FIGURE 5

In his final paper Professor Brown wrote that each time they found something unexpected they first questioned the reliability of the results. After establishing the results were correct, these were filed away until they saw similar results in other women. Sometimes it took years before this happened.

There were many studies, all bringing new information and more understanding.

Two papers from 1959[3] and 1962[4] brought a greater understanding of bleeding patterns.

Menstruation, that occurred after ovulation, and the two bleeds that are a result of anovular follicular activity. Withdrawal bleeding follows fluctuating anovulatory oestrogen secretion as the oestrogen values are falling, whereas breakthrough bleeding occurs while the oestrogen levels are elevated. This can occur during the fertile phase as the oestrogen levels are rising and stops as the oestrogen levels go even higher. Breakthrough bleeding can also occur as the oestrogen levels are raised and constant.

In 1975 a study[5] was undertaken looking at normal ovulating women compared to cycles of women with known ovulatory dysfunction. The results were subjected to statistical analysis in order to determine the number of oestrogen and pregnanediol tests required to determine the ovulatory status of the woman.

This study also determined the level of pregnanediol needed to confirm ovulation. Pregnanediol values exceeding 2mg/24hrs (9µmuol/24hrs) confirm ovulation.

It was also reported a single test – for either oestrogen or pregnanediol - was only useful in two situations. Oestrogen in the amenorrhoeic woman – if still low then confirms no ovarian activity. Pregnanediol in the women with regular cycles 4 – 8 days prior to menstruation. The latter has since been shown to not always be useful in determining the woman's fertility status.

Later studies were used to establish the relevant pregnanediol values for each of the cycle types. (Figure 6)

Cycle Type	Pregnanediol Values
Fertile Ovulatory	> 13.5µmol/24hrs
Short Luteal Phase	> 13.5µmol/24hrs and < 11days
Deficient Luteal Phase	8.5 – 13.5µmol/24hrs
Luteinised Unruptured Follicle	4.5 – 8.5µmol/24hrs

FIGURE 6

1978 Jim published the FSH threshold and intermediate level hypothesis[6].

He also made mention of the "deficient luteal phase" but there was no accompanying pregnanediol values at this stage, that came later.

The threshold level is required for follicle recruitment and for the beginning of the rapid growth phase.

For the follicles to continue to grow and for a dominant follicle to emerge, the FSH must continue to rise to the intermediate level.

This is how it was reported and remained unchanged even as more information was gathered and there was a greater understanding of the mechanics.

- FSH production by the pituitary hunts upward until it reaches the threshold requirement of few of the most sensitive follicles.
- The change in FSH levels is slight to ensure that only a small number of follicles are recruited.
- These recruited follicles begin their rapid growth phase.
- After a few days of growth, the oestrogen levels begin to rise providing the message the threshold has been reached.
- The FSH now continues to rise to the next level the intermediate.
- A dominant follicle will emerge from the group of the recruited follicles.
- The follicle contains granulosa cells which are the oestrogen producing cells, as the follicle grows the number of granulosa cells increase and the oestrogen levels now rise rapidly. The granulosa cells contain the FSH receptors, as the follicle grows, its use of FSH is more efficient.
- The follicle now requires less FSH to continue to grow and the levels fall below the threshold level of all

the less advanced follicles. The less advanced follicles die or atrese while the dominant follicle continues to mature and is now receptive to LH.

As you can see this is quite complex and shows the brilliance of Jim Brown to work this out.

Let us continue the journey with the dominant follicle.

The high levels of oestrogen produced by the dominant follicle feed back to the hypothalamus which in turn sends the message to pituitary to release LH. This is the beginning of the ovulatory process.

The cells within the follicle change as they prepare the follicle for ovulation. That is, they luteinise. The change in the cells is responsible for a small rise in progesterone, even before ovulation. At the same time there is a fall in oestrogen signalling the end of the rapid growth of the follicle.

36hrs after the beginning of the LH surge ovulation occurs. The ruptured follicle is now transformed into the corpus luteum. Now progesterone production is doubling each day, and there is a second rise in oestrogen both produced by the corpus luteum.

If there is no pregnancy, the demise of the corpus luteum causes a fall in both progesterone and oestrogen and the woman will menstruate.

Now we can see the brilliance of our creator as well!

There were many studies conducted throughout the different life stages of women.

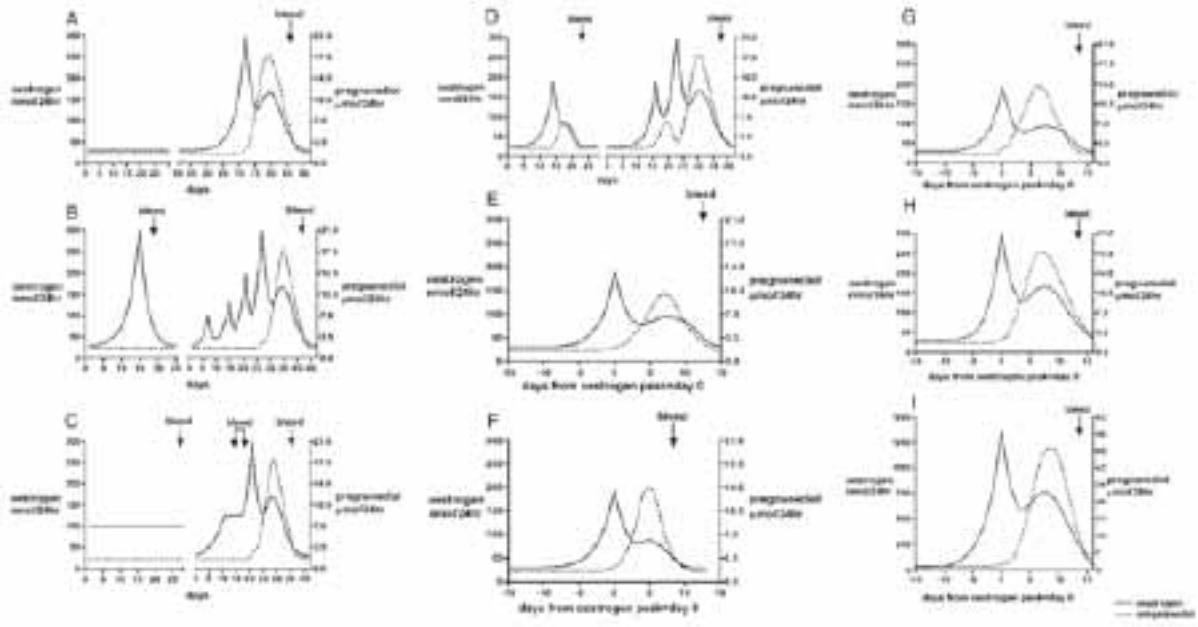
Menarche, breastfeeding, menopause - all these studies showed the same cycle variations.

J.B.Brown et al; *Oestrogen and pregnanediol excretion through childhood, menarche and first ovulation*; J.Biosoc Sci. Suppl.5 (1978) 43–62

J.B.Brown, P.Harrisson and M.A. Smith; *A study of returning fertility after childbirth and during lactation by measurement of urinary oestrogen and pregnanediol excretion and cervical mucus production* J.Biosoc Sci. Suppl.9 (1985) 5-23

Brown JB, Harrisson P, Smith MA, Burger HG; *Correlations between the Mucus Symptoms and the Hormonal Markers of Fertility Throughout Reproductive Life.* Melbourne: Advocate Press and Ovulation Method Research and Reference Centre of Australia, 1981.

I would now like to share with you Jim's published work on the various types of ovarian activity.



A - No ovarian activity. The FSH remains below the threshold therefore there is no follicular growth. As there is no follicular growth the oestradiol levels remain low. Unless the woman is in a permanent state of

amenorrhoea, as in menopause, then a fertile ovulatory cycle may follow.

B - Anovulatory follicular activity, no LH. This time the FSH rises to the threshold continuing to rise to above the intermediate. Follicles develop just as we saw in the earlier slide in the ovulatory cycle. However, there is no LH released and therefore no ovulation.

As the follicles are recruited and one becomes dominant, so we see a rise and peak in oestradiol. As there is no ovulation this will result in follicle atresia, the oestradiol levels fall. The woman may experience an oestrogen withdrawal bleed. This may occur several more times before the woman has an ovulation.

C - Anovulatory ovarian activity with constantly raised oestrogen excretion. This is also another type of follicular activity that does not progress to ovulation.

Unlike the previous example this time the FSH level arrests at the threshold and does not reach the intermediate. There is no dominant follicle. As the FSH rises above the threshold and remains there, many follicles are recruited resulting in constant raised oestradiol levels. The woman may experience a breakthrough bleed at this time. Most commonly the FSH mechanism corrects itself and progresses to ovulation.

It is possible that the woman may experience further breakthrough bleeding, this time during the fertile phase, as the oestrogen levels are rising.

The variants we have looked at so far have involved the FSH. The LH mechanism is the last to mature in the young girl but the first to wane in the older woman. What happens if the LH mechanism is faulty?

D - Luteinized unruptured follicle (LUF). The FSH reaches the intermediate level, a dominant follicle emerges. There is a rise in oestrogen, and this triggers the release of LH. In this case the LH surge is insufficient to cause ovulation, but it does cause changes within the cells of the follicle which then produces progesterone. The levels are slightly raised for a short time.

As the follicle atreses and the oestrogen levels fall, the woman may experience bleeding. It is also possible that she does not bleed but proceeds to ovulation. Professor Brown explained this in his paper "It seems that a follicle which is not going to progress to ovulation is recognized and its place is immediately taken by another follicle that is 'waiting in the wings'."

E & F - Ovulation followed by a deficient or a short luteal phase. In this variant, it is still the LH mechanism that is at fault.

Let's look at the deficient luteal phase (E) first. Follicles are recruited, a dominant follicle emerges and races towards ovulation. This time the LH surge is sufficient to cause ovulation but insufficient to produce a fully formed corpus luteum resulting in a deficient luteal phase.

A deficient luteal phase is one where the progesterone levels are above that of the LUF but below that of the fertile ovulatory cycle. As ovulation has occurred the following bleed is menstruation.

The short luteal phase (F)- follicles are recruited, a dominant follicle emerges and races towards ovulation. Once again it is the release of the LH that is faulty - the LH surge is sufficient to cause ovulation but insufficient to produce a fully formed corpus luteum resulting in a luteal phase of 10 days or less.

The progesterone levels reach those of the fertile ovulatory cycle but fall prematurely. Once again menstruation will follow.

Both deficient luteal phase and the short luteal are infertile cycles.

G & H - Fully fertile ovulatory cycle - now the FSH mechanism and the LH mechanism are both fully functioning. Everything proceeds in a well-ordered sequence resulting in a fertile cycle. Only this type of cycle is capable of producing a continuing pregnancy.

No ovarian activity – follicular activity, no LH – Luteinised Unruptured Follicle – Ovulation with an inadequate luteal phase – fully fertile ovulatory cycle.

This is the sequence that occurs pre and post menarche, during breastfeeding and weaning. If the woman

experiences stress, once the stress is removed, she may also experience some of the variants described.

The reverse may occur – when the woman traverses from fully ovulatory cycles to amenorrhoea. This can occur as the woman approaches menopause or during times of stress. This could include the physical stress the elite athlete puts on her body during intense training.

Continuum is defined as a continuous sequence in which adjacent elements are not perceptibly different from each other, but the extremes are quite distinct. Professor Brown has termed this "The Continuum" because each step merges with the next. Whether it is the maturation of fertility or the demise of fertility the extremes are certainly distinct. No ovarian activity versus fertile ovulatory cycle. Infertility versus fertility.

It is said a man with a vision talks little but does much, finds strength from inner convictions, continues when problems arise.

Millions of women throughout the world have benefited from this man with a vision. He did not shy away from the difficult but embraced it, always wondering why. It was this dedication and commitment that lead to the understanding of the Continuum of Ovarian Activity and the cycle variants.

We owe him a debt of gratitude.

In loving memory of Professor Emeritus James B. Brown MSc (NZ) PhD (Edin) DSc (Edin) FRACOG

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