The Billings Ovulation Method® in the service of knowledge, love and science

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This paper is a tribute to outstanding research about the Billings Ovulation Method®: it is a fact that the Billings Ovulation Method® has been subjected to more scientific research of the highest standard than any other method of regulating fertility, natural or otherwise, and it is now essential knowledge for the medical profession. [1,2,3,4,5]

The late respected director Anna Cappella was a tireless and passionate supporter of the Billings Ovulation Method®, as well as a friend and collaborator of Drs John and Evelyn Billings: the Centre on Natural Fertility Regulation (NFR) was born, from their partnership, at the Catholic University of the Sacred Heart in Rome, where couples have searched and found qualified professional advice on this Natural Method and a careful approach to the values of the person, respectful of the ethical issues related to the answers and reasons of the Magisterium with regard to sexuality and fertility. [6,7]

At the Centre we had the opportunity to meet Professor Erik Odeblad and Professor James B. Brown on several occasions and we've learned from them much about research on NFR, including studies on cervical mucus and on the hormonal patterns revealed by the Ovarian Hormone Monitor when used in different situations of the woman's fertile life. [8,9]

An expression that Lyn Billings used to introduce Professor Brown at a conference in Rome was very impressive: "All he will say to you is true" and the attendees were surprised by hearing from him that, during her fertile life, a healthy normal woman could have not more than 50% - 60% of cycles with the potential to achieve pregnancy. In that time, when the conventional wisdom was driven by the contraceptive mentality, his statement raised the paradox and the contradiction of such behaviour. [10,11]

Brown was elaborating the structure of his Continuum of Ovarian Activity, thanks to 850,000 hormone assays performed by the Ovarian Monitor, and to the contribution of many Billings Ovulation Method® users and Billings Ovulation Method® teachers in the world. (Figure 1)

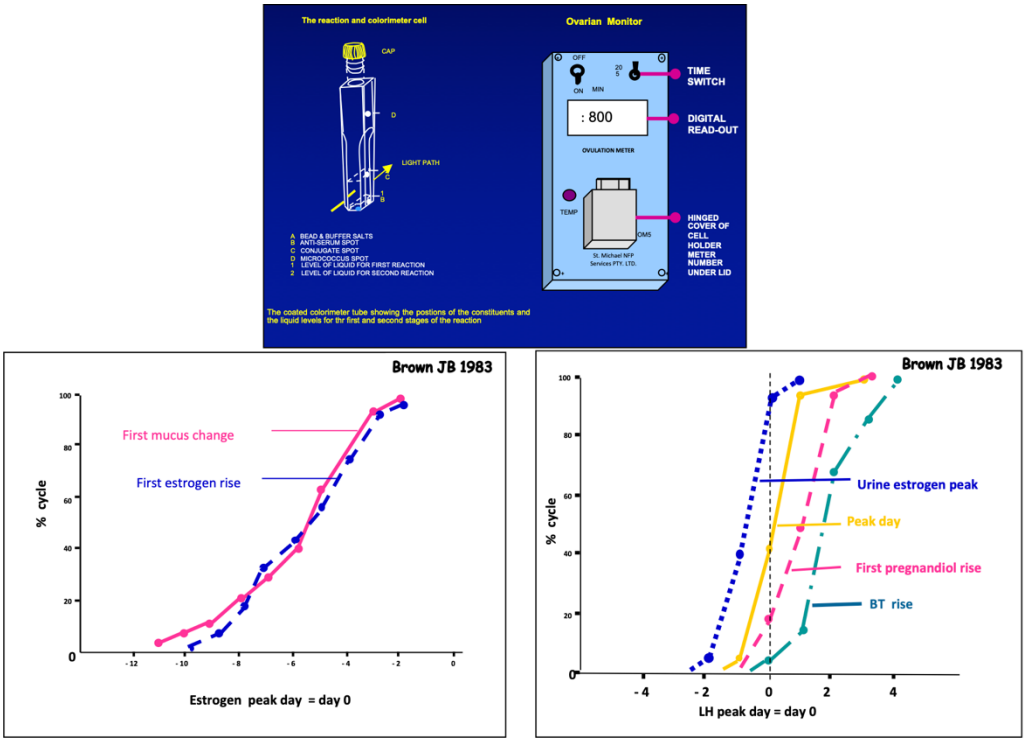

Figure 1. Hormone levels and mucus symptom correlation studied by Professor JB Brown.

There are many recent scientific publications of his studies, and the latest opens up interesting prospects for investigation on the variants of the cycles, that is the 40% of cycles with more complex hormonal patterns, affecting women of fertile age. [12,13,14,15]

The ideal cycle presents a normal pre-ovulatory infertile phase, characterized by low estrogens, a single preovulatory oestrogenic peak, a single follicle which becomes dominant and ovulates and a luteal phase adequate to sustain a pregnancy. All these events with this modality happen in about a third of normal ovulatory cycles. If only one of the aforementioned events undergoes a change, the cycle also undergoes an amendment of its characteristics and potential fertility.[16]

During the foetal life, the oocytary patrimony, which is present from the 5th week of intrauterine life, reaches its highest level with about 6-7 million follicles, around the 20th week of gestation. Later this number gradually reduces so at birth there are one million to two million follicles (which becomes 300-500 thousand at the time of puberty). Of these, only 300-400 will become eligible to ovulate throughout the whole fertile life of the woman.[17]

The progressive reduction in the number of available oocytes is accompanied by a progressive reduction of their quality i.e., of those biological aspects related to the ability to give rise to an evolutionary pregnancy. Folliculogenesis is a complex process that begins cyclically at least 5 months earlier (about 150 days) within the ovaries of fertile women. The initial part of this process is hormone-independent, i.e., not dependent on FSH.

At the end of the luteal phase of the previous cycle and the beginning of the follicular phase of the next cycle, there is a period called “Recruitment phase”. The luteal progesterone plays an inhibitory effect on the development of follicles in this phase. The number of follicles recruited, under optimal conditions, is about

10 - 20 in both ovaries. At the beginning of the follicular phase of the next cycle, a small group of follicles is selected from this cohort (“selection”) to continue to grow. The selected follicles prevent atresia as they acquire a greater number of receptors for FSH and LH. This stage is followed by a period called “Dominance phase” during which all the selected follicles, except one, undergo atresia. The only remaining follicle, called “the Dominant”, evolves to a mature follicle, and finally ovulates. (Figure 2)

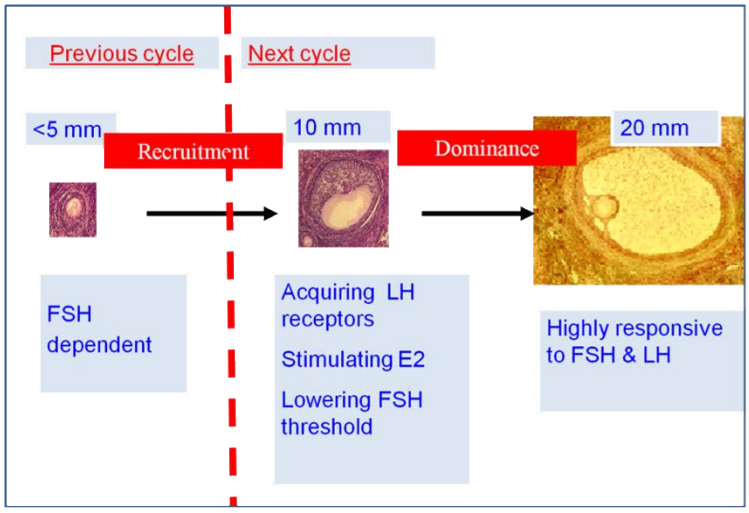

Figure 2. The end phases of folliculogenesis

This theory includes “waves” of follicles which, from the quiescent primitive stage, succeed continuously in the growth phase throughout the menstrual cycle. The final wave of follicular development is ovulatory, while previous ones are anovulatory. An integration of this theory is the “propitious moment”, i.e., a single follicle grows and is made ready in a privileged hormonal moment: the peak of gonadotropins induces ovulation of that follicle that was ready exactly at the right moment. [18,19,20]

Professor Brown, with the concept of “FSH threshold” has greatly clarified the understanding of folliculogenesis. As regards the “Selection”: only those antral follicles present at the moment at which the FSH exceeds its “threshold” in the early follicular phase, can move toward maturation.

With regard to the “Dominance”, he has checked that there is only a narrow margin between the effective level and one, above which, an excessive response is obtained with multiple ovulations. When this happens, there is an extension of the length of the “dominance phase”. (Figure 3)

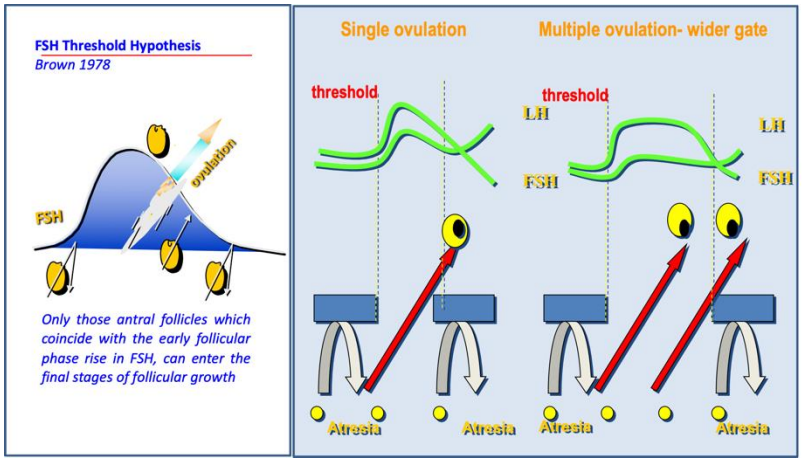

Figure 3. Professor JB Brown's "FSH Threshold" hypothesis

These facts were acquired by hormonal and ultrasound studies of cycles with ovulation induction using gonadotropins. [21,22,23]

It is well known that even in the "ideal" cycles there is a physiological variability regarding respectively the baseline levels of estrogen, the amplitude of the preovulatory estrogen peak and the progesterone optimal value in the mean-luteal phase. Many other interesting variations can be expected in the "variants" cycles, even when ovulatory.

It is only right to recall how recent ultrasound studies confirm the statements of Brown on the prediction of the percentage of optimal/standard cycles and of the "variants", in which there are multiple follicular waves, before that one which comes to ovulate.

In these cases, the increased inter-ovulatory interval is a consequence of the longer duration of the pre-ovulatory follicular phase, where successive waves of follicles start to grow, then regress, leaving space for the next wave. The last wave is ovulatory: as is shown by the largest ultrasound size of the ovulatory follicle, which is larger than any previously selected anovulatory bystander waves.

Moreover, Professor Brown informs us that in approximately 50% of cycles, several follicles jostle for dominance, the first dominant one may fail to ovulate and another "waiting in the wings" follicle can take its place reaching dominance. This may occur several times before ovulation is achieved. When this finally happens, further recruitment of follicles for ovulation in that cycle is positively inhibited.

These estrogenic peaks occur when the hormonal levels are corresponding to the baseline of the follicle destined to ovulate and they impede the detection of the start of its "rapid growth phase". It would appear that these early follicles, with the egg cells contained within, are imperfect and their rapid replacement ensures that only a fertile ovulation may occur at each cycle. (Figure 4)

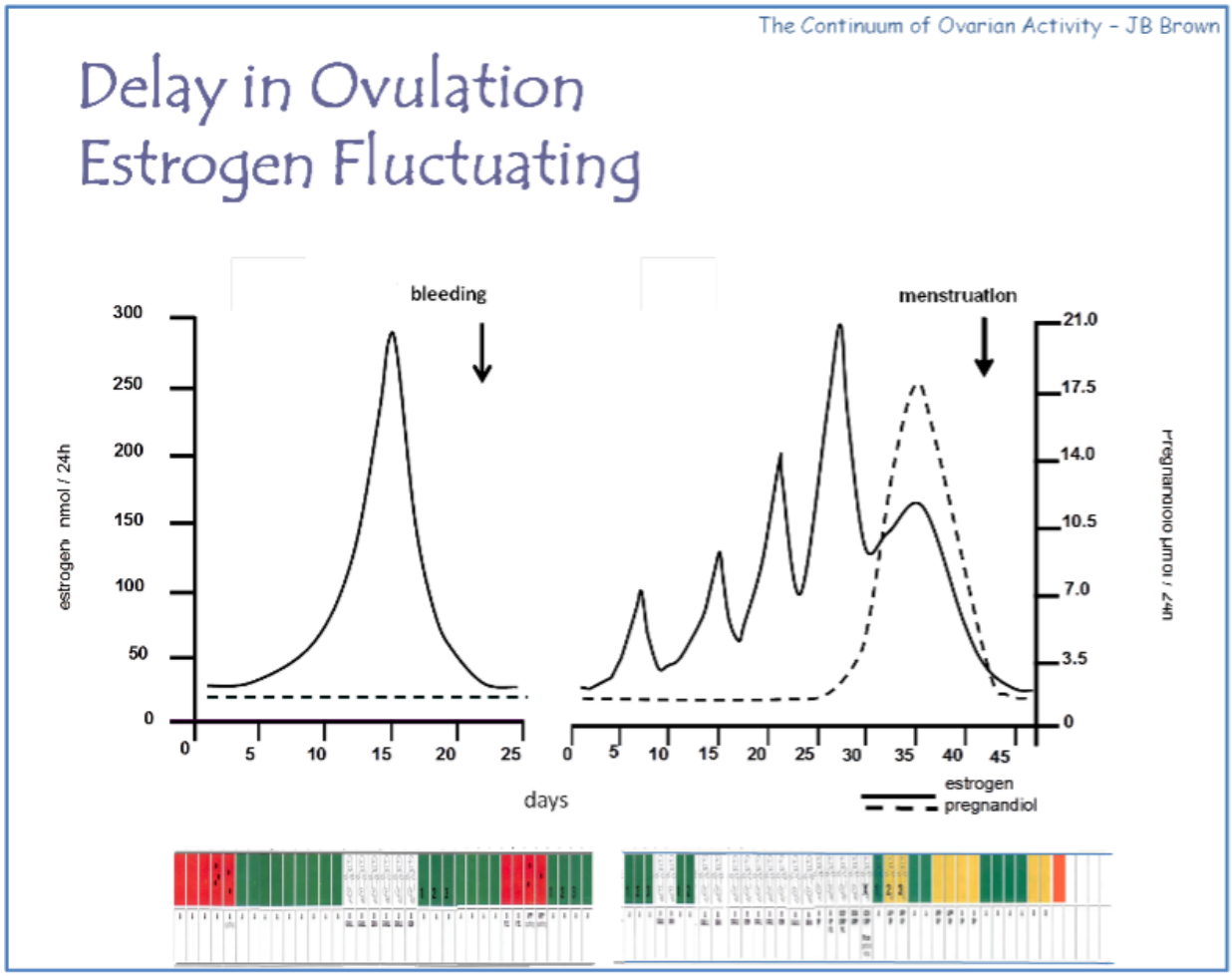

Figure 4. Correlation of preovulatory fluctuating estrogens and mucus symptom.

In gonadotropin treatment it is possible to use this phenomenon to eliminate a follicle, which presents characteristics of imperfect growth, and to ensure a natural selection of another follicle, recruited from the same group, with better characteristics, thus increasing the chances of pregnancy.

These early oestrogen peaks are lower than the final ovulatory peak, and when several early peaks occur, each succeeding peak is higher than the preceding one. A frequent feature of these early anovulatory oestrogen peaks is that they do not initiate an LH surge or a recognisable change in cervical mucus that precedes ovulation, and do not often result in sufficient endometrial growth to cause bleeding. It thus appears that the oestrogen produced is not as biologically active as the oestradiol produced by a follicle that ovulates and is therefore probably mainly oestrone or is derived from an androgen that is converted peripherally to oestrone. This is consistent with present concepts of steroid synthesis by ovarian follicles.[23]

The diagram and the correlated explanations stimulate two types of reflections. The first relates to the in vitro fertilization techniques, involving the fertilization of many egg cells obtained in the same cycle with hormonal stimulation, making the pickup without a distinction between the egg cells taken from antral ovulatory follicles or anovulatory ones. The second concerns the wonderful uniqueness in the ovulatory cycle by the symptom of the mucus Peak, which, alone, is able to allow the identification of a “fertile ovulation”, thanks to the effect of progesterone on the woman’s symptom.

Every natural method is based on a specific methodology and teaching experience. As there are different reading systems for thermal curve, so there are different ways of detection and interpretation of the mucus symptom: that is, there is no mucus symptom and “mucus Peak” equal for all the methods. [24,25]

We are really lucky to know a Method that is based on a so precise and refined parameter which reflects the whole ovarian activity and, due to the effects of estrogen on the cervix, to be able to distinguish the ovulatory Peak from other signals. Correct knowledge of the protocols of the Billings Ovulation Method® is important also to understand and explain the scientific papers regarding “statistical sensitivity”. (“Sensitivity” and “specificity” are intrinsic characteristics of a test that describe the diagnostic capability of the test). In stating that the “sensitivity” of the Peak in identifying ovulation is 86% compared with the higher percentage of ultrasound studies, it would be useful to investigate whether, in those studies that integrated Billings Ovulation Method® cycles with other methods, the distinction between the Billings Ovulation Method® Peak, which is recognised by specific criteria, and other “peaks” was made explicit.[26,27]

The studies conducted at our Centre seek to better investigate the correlation of any anomalies (that the woman, even occasionally, identifies thanks to the mucus symptom detected according to the Billings Ovulation Method ®) and the underlying ovarian situation.[28,29,30,31]

There are special situations in the fertile life of a woman where the cycles undergo physiologically interesting variations, from ovulatory to anovulatory ones, sometimes gradually, sometimes occasionally. The mucus symptom as taught by Billings Ovulation Method® recognizes, among a normal cervical function, many types of cycle anomalies, e.g.: the absence of the mucus Peak, - the presence of patches of mucus and bleedings in the preovulatory phase - the presence of short luteal phases and bleedings in the postovulatory phase. Further we can detect contextually the absence of ovulation, the fluctuations of ovarian activity in the absence of ovulation, intermenstrual bleeding, and luteal insufficiency.

In our study of 90 individual cycles, monitored with urinary assays, we have distinguished a group with normal ovulatory cycles, and a group that displays various types of situations with irregular duration and with different anomalies of the cycles.

An example of a cycle variant of this series might look like that which shows the first ovulation of a breastfeeding woman during weaning. There is an evident extension of the pre-ovulatory phase, delayed ovulation, and the short duration of the luteal phase <11 days. (Figure 5).

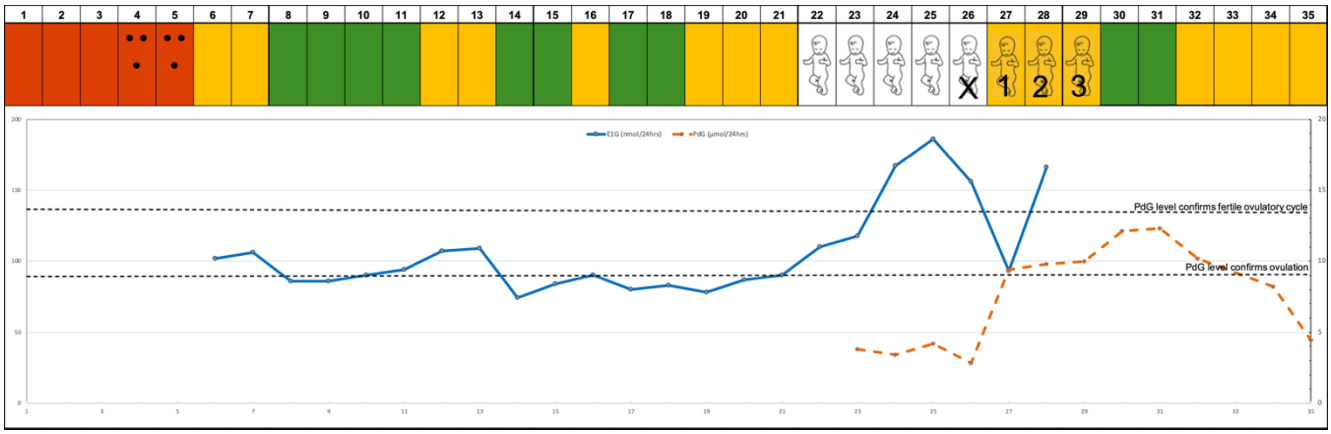

Figure 5. Cycle variants. Breastfeeding: hormonal monitoring of the first ovulation during weaning, followed by inadequate luteal phase.

Another case is that of a woman who has had to undergo cervical conization surgery a few months before. The poor mucus symptom does not allow identification of a Peak, but the hormonal assays detect ovarian activity with an estrogen surge, followed by progesterone deficiency. The drop in progesterone could be possibly responsible for spotting in subsequent days of the cycle. (Figure 6)

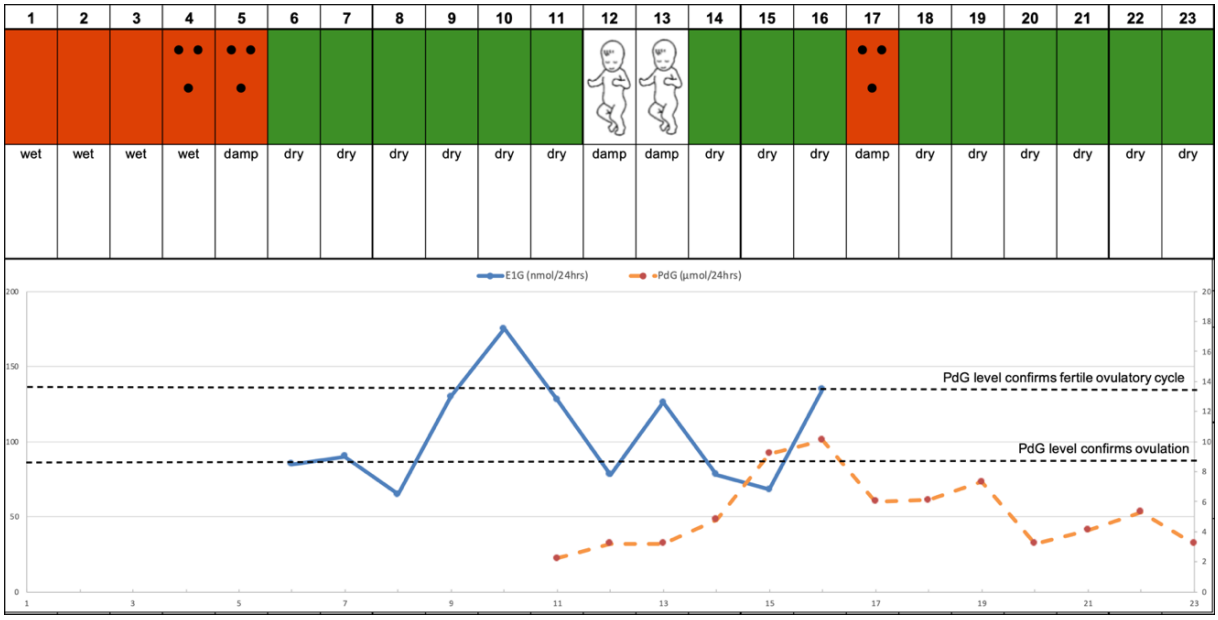

Figure 6. Cycle variants. 6 months after cervical conization; ovarian activity is present with estrogen peak in day 10, followed by progesterone deficiency. Spotting on day 17 may be result of drop in progesterone.

Several parameters have been correlated to the day “zero” of ovulation in all cycles: the parameters examined are: the day of the preovulatory oestrogenic peak; the day of mucus Peak by the Billings Ovulation Method®; the day exceeding the Pregnanediol cut-off and the last fertile day according to the Billings Ovulation Method®. These events follow each other in a fairly ordered way. The best indicator

related to the ovulation event is the mucus Peak, while the Ovarian Monitor - with assaying Pregnanediol-3-glucuronide - confirms the end of the fertile phase identified by the Billings Ovulation Method® (Figure 7)

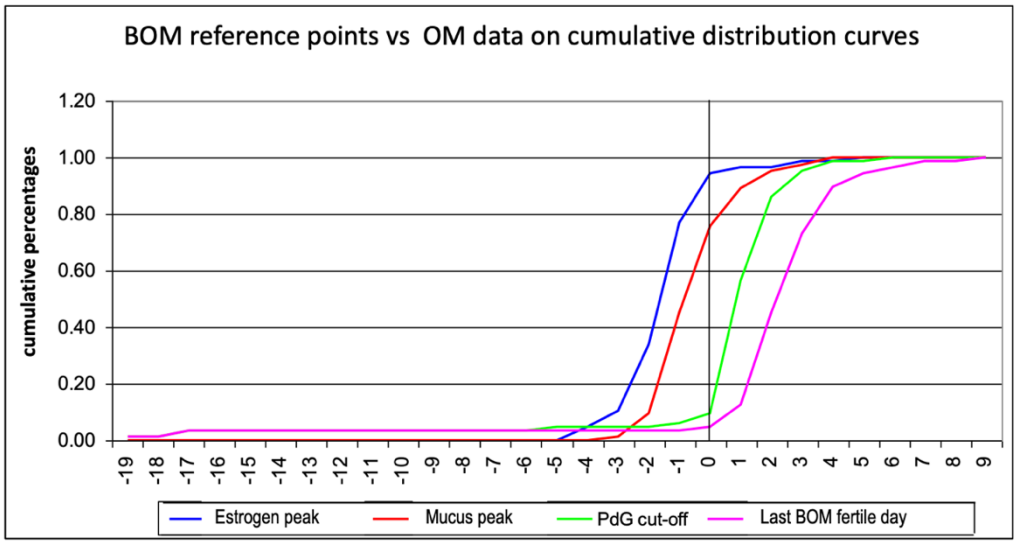

Figure 5. Correlation of mucus symptom by Billings Ovulation Method® and hormone monitoring of ovarian activity by Ovarian Monitor in 90 independent cycles. Correlation of the Billings Ovulation Method® and Ovarian Monitor reference points with ovulation day (day 0)

By comparing the single variables and distinguishing two women groups (normal and abnormal cycles), we may notice that these events tend to be “retarded” in the group with irregular cycles. There is a significant difference especially referring to the day of mucus Peak. (Figure 8)

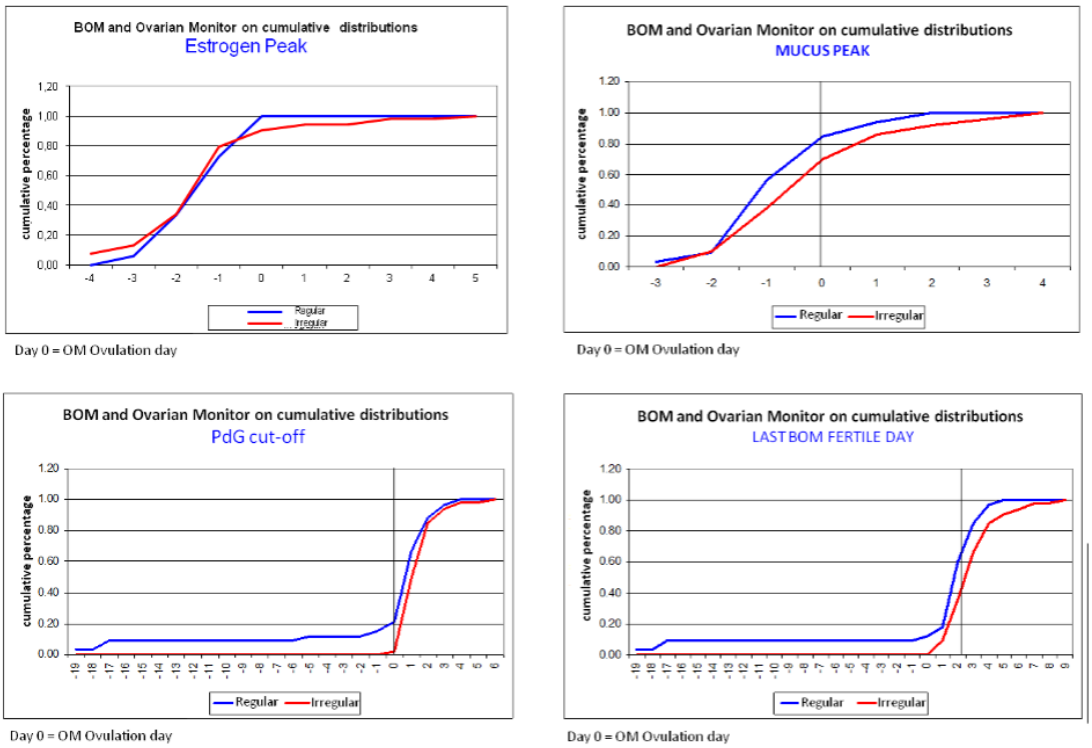

Figure 6. Study of luteal function in the 2 groups. When compared to the control group, the group with irregular cycles present a higher frequency of luteal inadequacy (midluteal PdG <9umol/24h) and a higher frequency of short luteal phases (<11 days).

Having the chance to investigate the luteal function, it shows that the group with abnormal cycles presents a higher frequency of luteal insufficiencies (with values of PdG < 9µmol/24h) and greater presence of short luteal phases (<11 days) compared to the control group. (Figure 9)

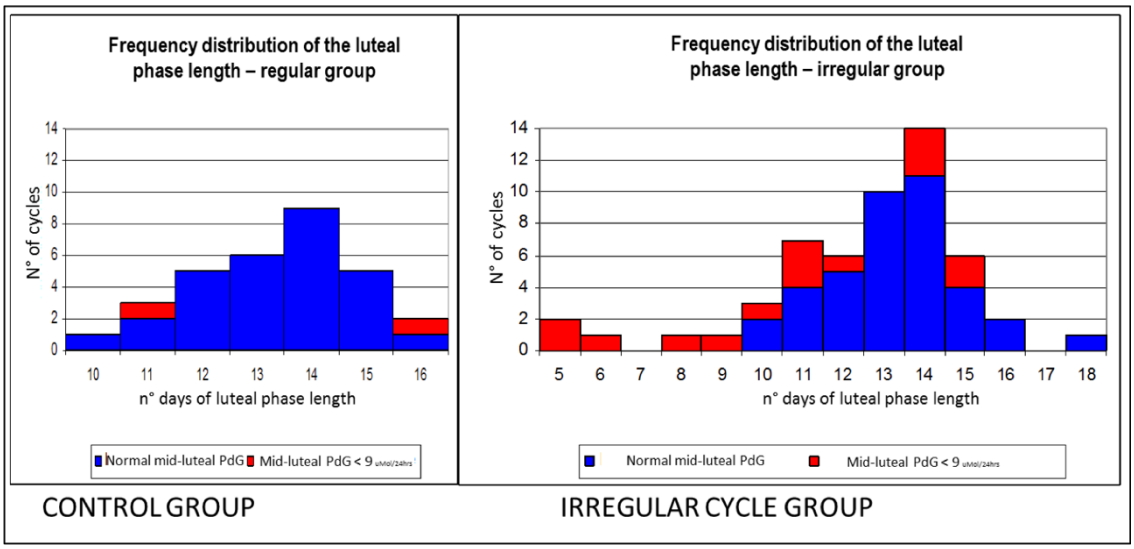

Figure 7. Comparison of the different parameters in two groups of women (regular and irregular cycles).

Assisting Conception – Using the Billings Ovulation Method® as a Diagnostic Resource

The previous data relates to different situations of fertile life, but our aim was to compare normal women's cycles with those of women in conditions of infertility, both "physiological" as premenopausal, and effective, as in the case of those who are looking for pregnancy.

In the Billings Ovulation Method® teaching service and in our pastoral care, we try to offer help and empathy for one of the sufferings with which we today come increasingly in contact, and this is "infertility". The couples who turn to our Centres are helped, through a process of awareness, by listening to them, providing human support as well as qualified professional advice on Billings Ovulation Method®. Helping the couple to identify ovulation and to use this optimum couple fertile time for intercourse is sometimes sufficient to achieve pregnancy.

Concerning the premenopausal woman, it is not necessary to recall the main diagnostic symptoms - which however have to be investigated in all women seeking pregnancy - but rather to point out that the main cause of infertility in developed countries is the women's advanced age. Over the years, it has been seen that the average age of first pregnancy has gradually increased. In Europe, Italy has an unenviable record of being a population with a low birth rate, insufficient to ensure a generational turnover, and with an older population. In the last decade the number of children appears to be a little increased, due in part to migration from outside Europe. [32,32]

As age increases, there is a gradual decline in fertility, characterized by the reduction in numbers of available oocytes and by the increased pool of those of low quality. There is a reduction of the "ovarian

reserve", that is, of those follicles able to respond to the FSH stimulus at a given time. If to these factors we also add the opportunity of an endometrial deterioration the risk of age-related infertility can be well understood. [34,35]

The progressive shortening of the menstrual cycle is an indicator which is not difficult to detect in the interview with the woman, but for an adequate diagnosis it must be referred to hormonal and ultrasonographic examinations. The increase of FSH, which seeks to "force" the depleted ovary, is matched by the decrease of factors produced by the same ever fewer follicles, such as Inhibin B and Anti-Müllerian Hormone (AMH). These factors can be dosed in plasma. A good ultrasound evaluation enables you to see objectively the ovarian reserve. [36,37]

The Anti-Müllerian Hormone is related to the pool of primordial follicles in women, and has, together with the Inhibin, the ability to slow down the action of FSH during folliculogenesis. Its circulating levels decline with age and are not influenced by the phase of the cycle. It is a useful diagnostic indicator also in Polycystic Ovarian situations, where it is increased.

However, we must point out that a low AMH level has a predictive value of about five years regarding menopause time: this is the interval expected so that the woman's ovary will totally exhaust its reserve, if AMH begins to present low values. Ultrasound evaluation of ovarian reserve takes into account not only the number of follicles, but also ovarian volume and the blood flow. When available, the 3D ultrasound significantly improves the numerical counts of antral follicles. (Figure 10)

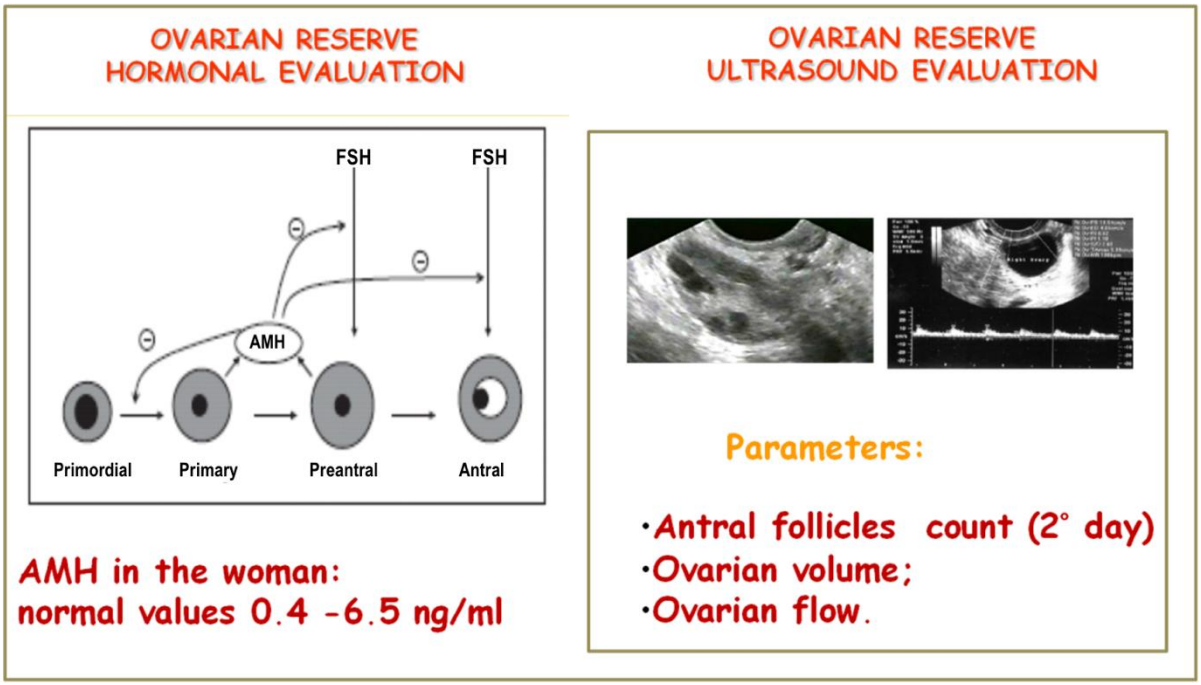

Figure 8. A correct evaluation of the ovarian reserve includes the simultaneous detection of two parameters: hormonal and ultrasound.

The pool of antral follicles consists of those able to respond to the “recruitment” by the FSH stimulation and is related to the ovarian reserve of primordial follicles. In women, an early ultrasound in the cycle (day 2) provides adequate numerical counts.

The Billings Ovulation Method® has the ability to make evaluations which are very close to those of clinical tests: this 47 year old woman presents a long preovulatory period with some signals of estrogenic stimulation, before there is evidence of an ovulation. The next cycle, even though it is ovulatory, is very short. Both cycles present an insufficient duration of the luteal phase and are infertile ovulations. (Figure 11)

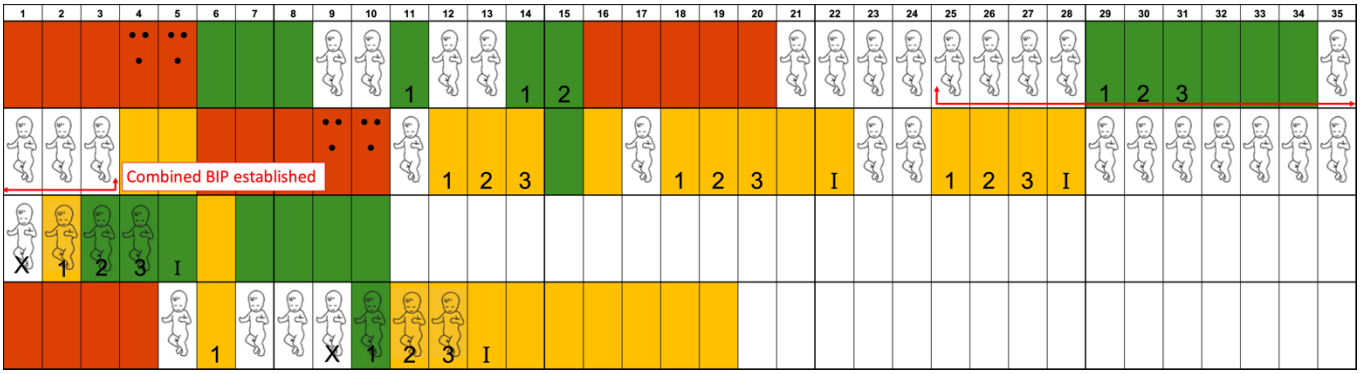

Figure 9. Cycle variants: Premenopause. Two consecutive ovulatory cycles (a long and a short one), both presenting luteal phase inadequacy.

These events are representative of early menopause, when we note - considering prolonged estrogen stimulation in the anovulatory periods - some rare ovulations, followed mainly by insufficient production of progesterone. This circumstance is named “relative hyperestrogenism”, which means that, in a general context of reduction in the ovarian hormones, the production of estrogen and progesterone is unbalanced in favour of the first.

Comparing the ovulatory cycles of the two “infertile” groups studied, some features are noted: a greater length of the cycles, with normal basal value of estrogens; the delayed day of ovulation especially in the infertile group; but it is the average value of the mid-luteal progesterone that reveals the inadequacy of these cycles. [38,39] (Figure 12)

	NORMAL	SD	PREMENOPAUSE	SD	P	SUBFERTILITY	SD	P
Nº	25		18			25		
Age	25 - 38		42 - 48			23 - 39		
Cycle length *(days)*	29	3.2	35 ↑	21.1	0.13	33 ↑	11.7	0.1
E1G baseline *(nmol/24h)*	126	30.5	126	26.4	0.96	129	34.5	0.7
Ovulation *(by OM)*	15	3.2	16	3.9	0.3	18 ↑	9.0	0.1
Luteal Phase *(days)*	13	1.2	12	2.0	0.008	12.7	3.0	0.2
Midluteal PdG *(µmol/24h)*	20.8	7.5	14.9 ↓	8.9	0.02	15.7 ↓	7.9	0.02

Figure 12. Comparison of ovulatory cycle characteristics by two different subfertility

The diagram explicates these results reporting also the value of the “statistical variability”, which allows a better interpretation of the mean values. For example, considering the length of the luteal phase, we can see how the group of women who suffer infertility, despite having an average similar to the other groups, has a much higher variability. In the diagram related to the length of the cycles, the premenopausal group has a greater length, with much higher variability than a normal one. (Figure 13)

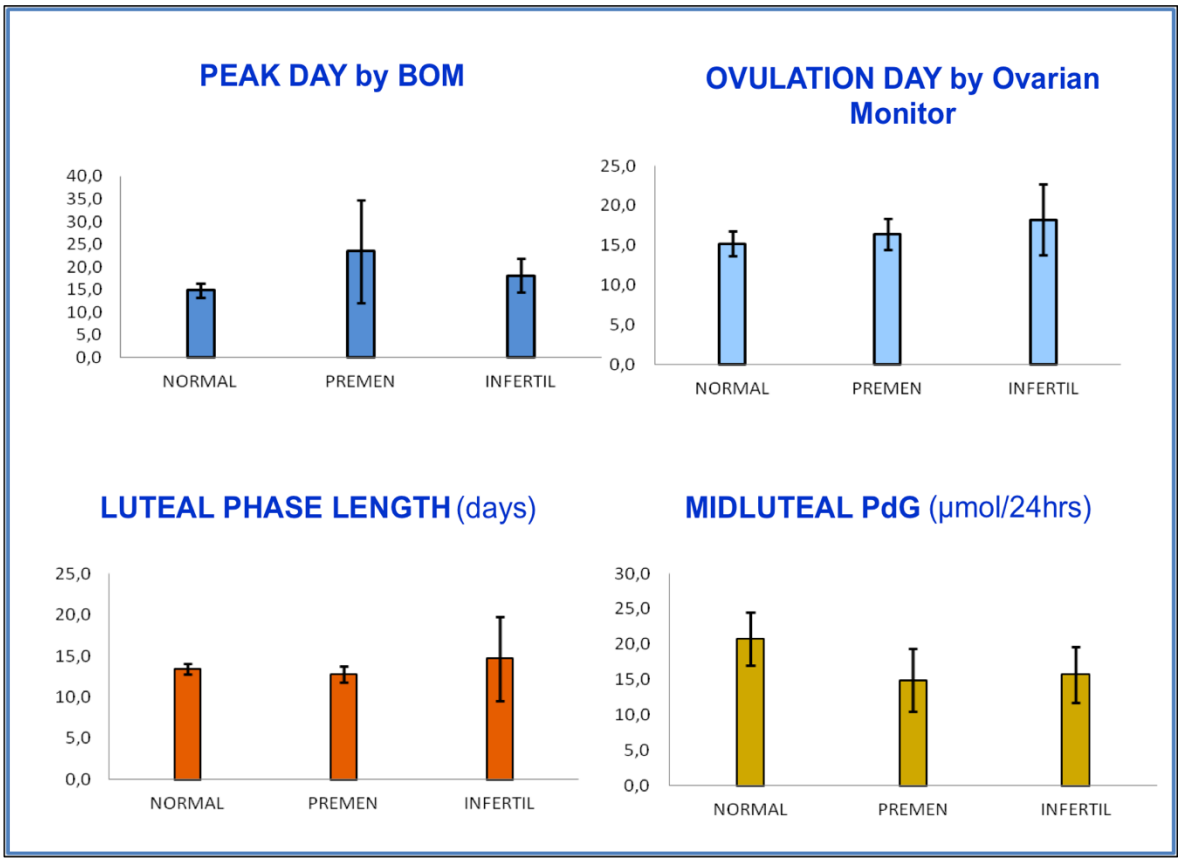

Figure 13. The diagram explicates the results reporting the value of the variability

The length of the identifiable fertile phase is almost comparable between Billings Ovulation Method® and the group with hormone assays, but less with other commercial products for domestic use.

Further extending the theme of infertility, we evaluated interesting data in addition to the ovulatory cycles in another series of 150 women. We took into account some prognostic factors correlated to the regularity/ irregularity of the cycle such as: age, eating habits, the previous use of hormonal contraceptives, the presence of pathologies interfering with fertility, the prior use of ARTs. [40,41]

Concerning the “age” factor, it is interesting to note that, in our study, younger women have more irregular cycles than those over 35yrs. (Figure 14)

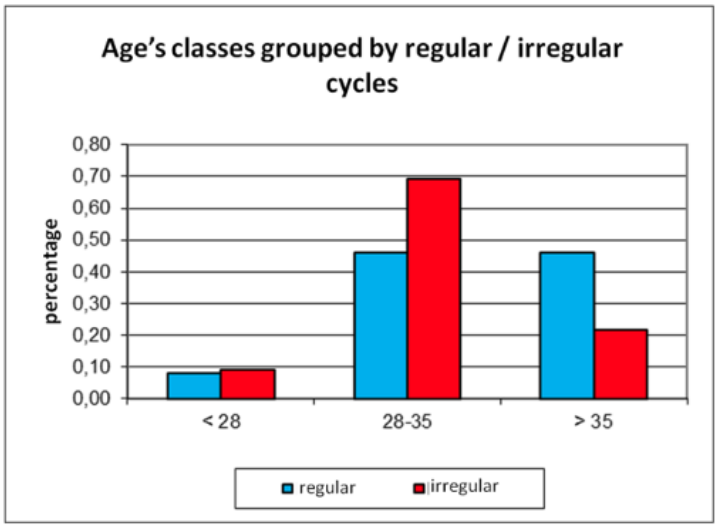

Figure 14. Among 28-35 yrs the presence of irregular cycles is greater, whilst among the over 35 yrs those with regular cycles are more numerous.

Today great attention is paid to lifestyles and to eating habits, and the Body Mass Index (BMI) is the set-point for distinguishing normal weight, underweight or overweight. In the studied cases, it seems excessive thinness affects more dramatically the irregularity of the cycle, rather than overweight. Indeed, among overweight women the number of those with regular cycles is higher. (Figure 15)

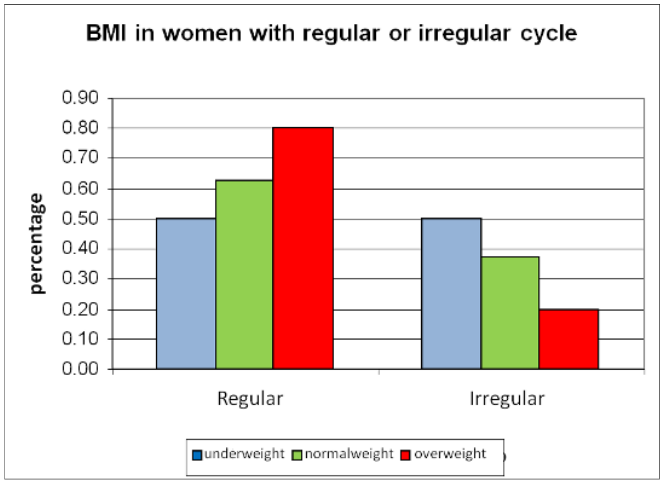

Figure 15. The increase in the BMI seems to correspond with the increased number of women who declare regular cycles and, vice versa, the decrease in the BMI seems to be more common in women who declare irregular cycles.

This finding is congruent with what is known about the influence that severe thinness has on life expectancy, compared to overweight. In the condition of thinness, further, small weight reductions dramatically reduce the life span compared to equivalent weight gain in obese subjects. Data regarding the lifestyles of the population obviously need to be interpreted correctly, avoiding generalizations, and should be placed in relation with environmental factors such as country or ethnicity. BMI distribution in the current Italian population (18 yrs and over) is: 3% underweight; 51.5% normal weight, 35.5% overweight, 10% obesity. [42] The previous use of oral contraceptives may impair fertility affecting the regularity of cycles: however, our study shows that women with regular cycles make a more frequent therapeutic use of the pill,

while women with irregular cycles make a more contraceptive use. On the one hand this contradiction requires a reflection on the doctors' role when prescribing these drugs, and on the other hand, a consideration of the women's awareness of their own fertility, especially for those who are looking for pregnancy. (Figure 16)

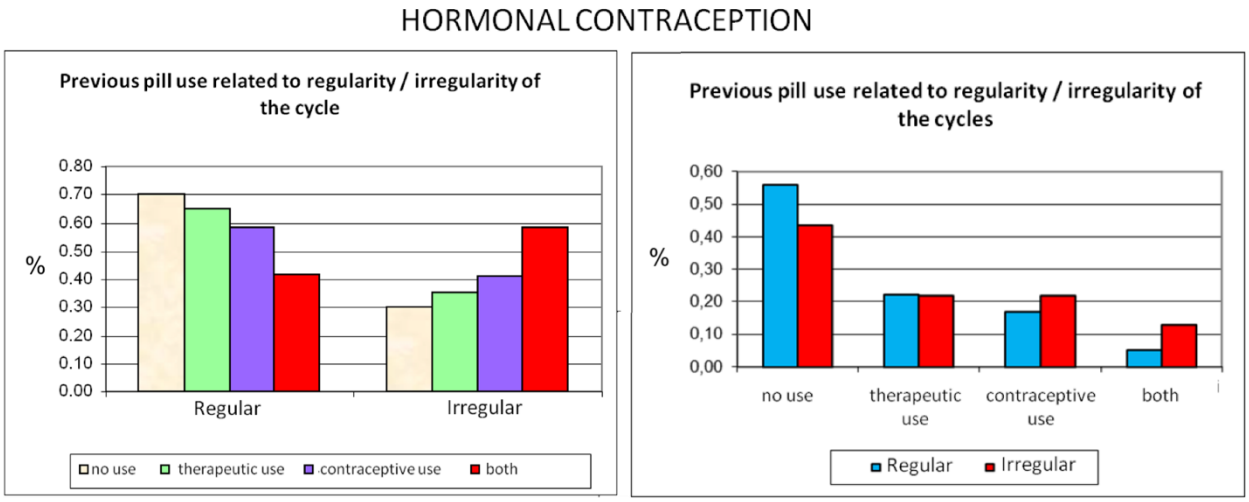

Figure 16. Women who never used the pill are more common among regulars, while those with therapeutic and contraceptive use are most concentrated among the irregulars. It should be noted the group who used the pill only for contraceptive purpose, most frequently declare irregular cycles.

In the presence of pathologies that affect fertility, this must be classified in female, male or both. Among couples without pathologies there is a slight majority of women with irregular cycles, to reinforce the fact that the irregularity is not synonymous with disease. Otherwise in couples with a regular cycle there is a slight prevalence of male pathologies. (Figure 17)

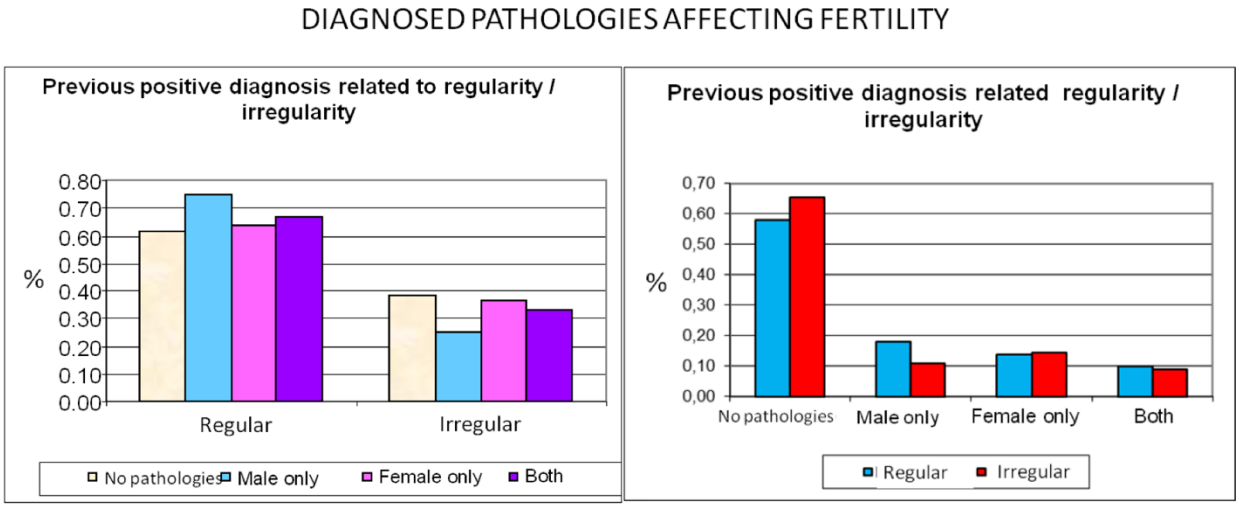

Figure 17. Among couples with regular cycles there is a slight majority of those with male diseases. Among couples without any diseases there is a slight majority of those with irregular cycles.

The role played by fertility awareness in the search for pregnancy has already been recalled, together with the importance of the support offered by the teacher in these cases: the results of the study confirm the importance of this role, in terms of success rates obtained (overall around 70%). [43,44]

When considering the time spent to achieve a pregnancy, the normal population reaches the rate of 75% within 6 months, while our sub fertile group obtained globally the same result in one year, which is equivalent to the duration provided by the study. In “infertile” couples who achieved pregnancy, the time to achieve using the Billings Ovulation Method®, is not much different between the two groups, with greater advantage of irregular cycles, presenting a peak of pregnancies after 3 cycles.

The Billings Ovulation Method®, achieved greater success in the group of couples with irregular cycles than with normal cycles: note, however, that the first group presented minor pathologies, especially male. (Figure 18).

The previous use of the pill represents a negative prognostic factor, as not only can it be correlated to a greater number of irregularities, but also to a lower percentage of pregnancies. The largest number of pregnancies are obtained in women, preferably with regular cycles, who never used the contraceptive pill. (Figure 19)

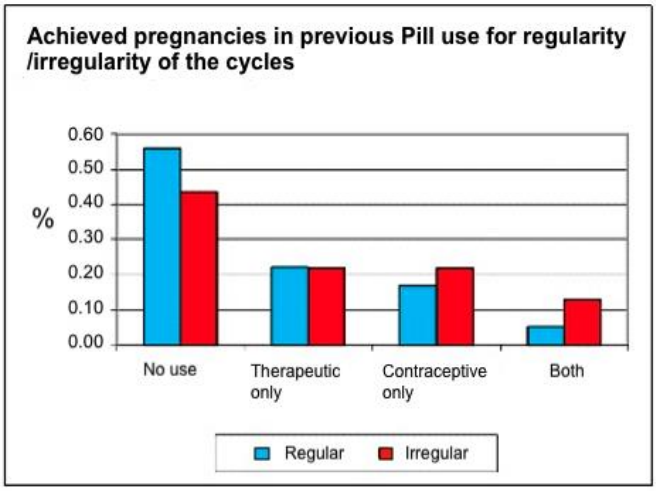

Figure 10. Pregnancy outcome: among couples who became pregnant with the BOM; those without previous use of the Pill prevailed, especially those with regular cycles.

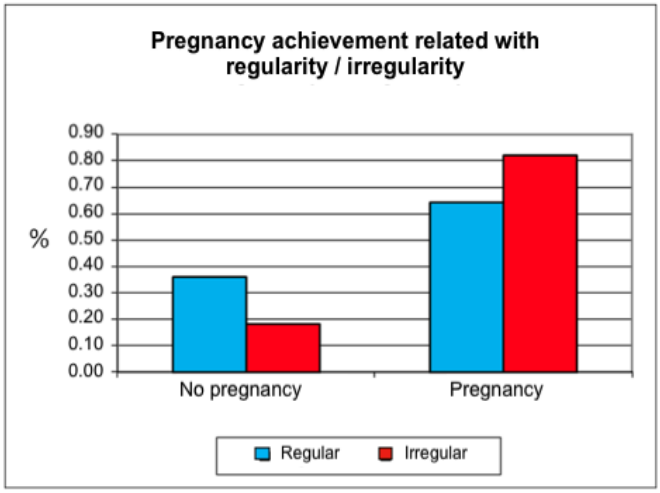

Figure 19. Pregnancy outcome: among couples with irregular cycles a successful pregnancy is more common than among those with regular ones.

In some couples’ histories, the previous use of ARTs was revealed. The two groups, with both regular and irregular cycles, had resorted in equal measure to IVF, but in terms of pregnancy obtained with the Billings Ovulation Method®, the group with irregular cycles again had the favoured results. (Figure 20)

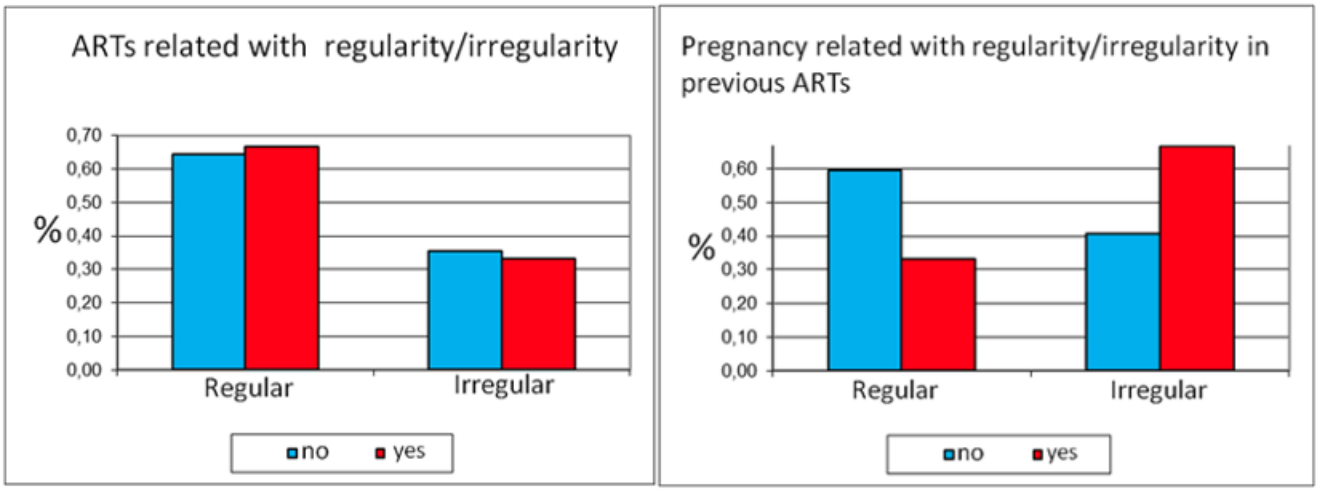

Figure 2011. Assisted Reproductive Technologies and pregnancy achievement: it seems there isn't any correlation between regular/irregular cycles and previous ART recourse, but among patients who achieved pregnancy with Billings Ovulation Method®, those with irregular cycles seem to be more numerous.

At the conclusion of our study we can make a few comments:

- couples with regular cycles tend to delay the learning time of the Billings Ovulation Method® and the start of medical investigations;
- previous use of the pill, both for therapeutic and contraceptive purpose, plays a negative role in terms of fertility;
- cycles presenting irregularities do not necessarily coincide with a pathological situation;
- use of the Billings Ovulation Method® favours situations with irregular cycles, with percentages of pregnancy equivalent to those of regular cycles;
- recording of the mucus symptom helps to identify abnormalities that, if correctly identified, allows a correct diagnosis and therapy.

In statistical works, the presentation of data does not allow us to know the individual couples' history, especially in our current era, when everything refers to "Evidence Based Medicine" and its standardized protocols. Despite that, two stories are particularly emblematic of the personal suffering and of clinical pathways conducted. The first couple, married for 10 years, had had four ICSI (Intra Cytoplasmic Sperm Injection) and one IUI (Intra Uterine Insemination) without success. The couple had started a spiritual process, in which information on the Billings Ovulation Method® was included. The approach with a qualified Billings Ovulation Method® teacher, had helped an early diagnosis of hyperprolactinemia, due to hypothyroidism, and metabolic syndrome. An appropriate therapy has, in a short time, improved the situation, with lengthening of the luteal phase, and achievement of conception, despite several other problems and stress, such as a bartholinitis and the removal of an endometrial polyp. The last cycle has given us Paul, named in honour of Pope Paul VI, whose beatification was celebrated by the couple in St. Peter's Square, only days before discovering the pregnancy. (Figure 21)

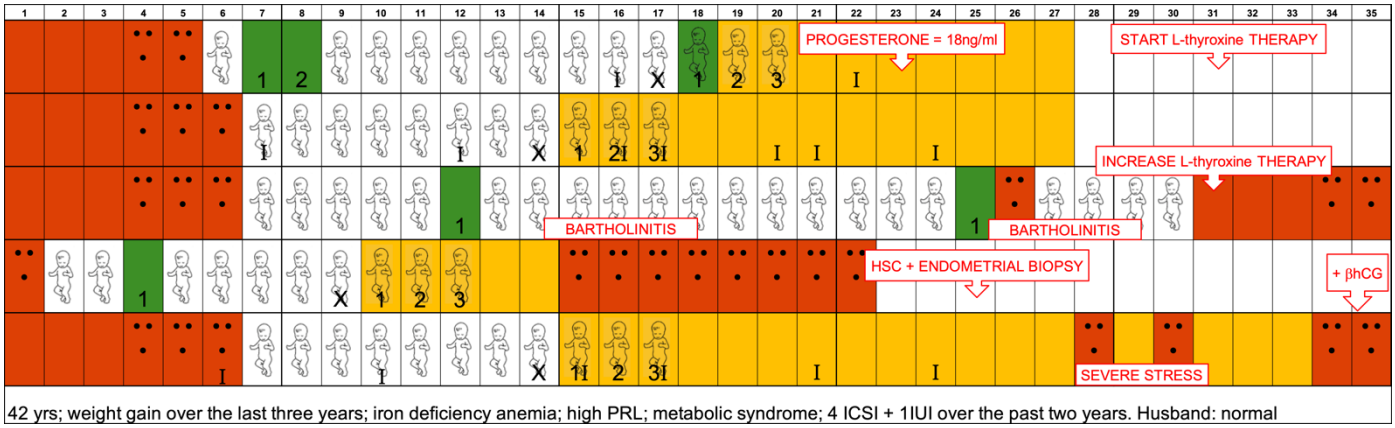

Figure 121. Pregnancy achieved with Billings Ovulation Method® after ARTs failure. Diagnosis of hyperprolactinemia due to clinical hypothyroidism, regressed with thyroxine replacement therapy.

The woman's current situation represents a breastfeeding pattern, where the hyperprolactinemia is physiological and causes the delay of ovulation. (Figure 22)

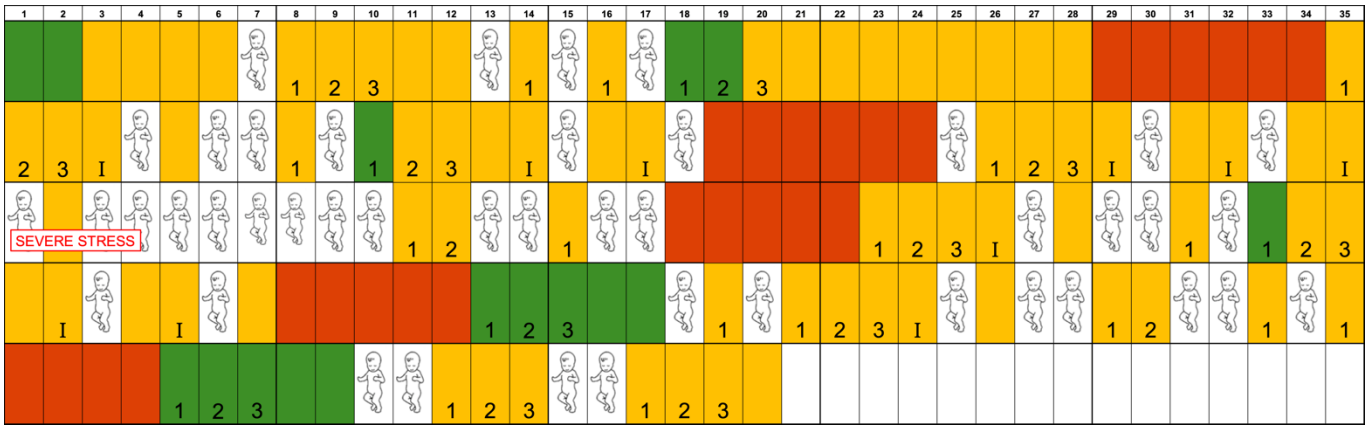

Figure 22. Cycle variants: following breastfeeding (physiological hyperprolactinemia)

In the second case both spouses have problems. The woman had gained weight in recent times and, despite the fact she was presenting relevant bleedings, which were resistant to anti haemorrhagic therapies and leading to anaemia, had been repeatedly subjected to ICSI interventions. After the beginning of learning Billings Ovulation Method®, she too had been diagnosed with hyperprolactinemia for hypothyroidism and the metabolic syndrome. Her husband was sent to andrological care. In their chart we note the improvement of the situation after treatment, but the couple had no pregnancy. Problems in the married life have pushed the woman to take antidepressants that, before long, compromised the beneficial effects of thyroid therapy and of the diet. However, the couple continues to record and keeps in touch with the teacher. (Figure 23)

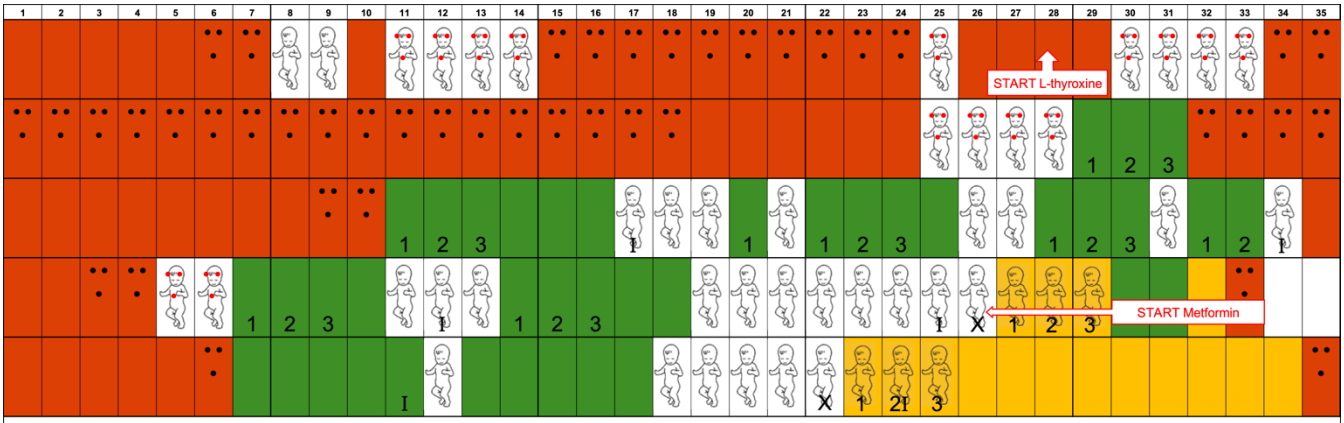

Figure 13. Couple wishing to achieve pregnancy after ARTs failure: another case of subclinical hypothyroidism with hyperprolactinemia.

To solve a problem of infertility, the teacher will have to take the couple by their hands and support them in deepening respect for each other. This is an important aspect of the teachers' role to foster such a way of thinking and leave couples not with a sense of despair but with a deeper love. It is possible that the teacher's task for this couple is not to help them in achieving pregnancy, but to help the couple to create a stronger bond, full of love, that makes them able perhaps to adopt other children in the world, who are unloved, abandoned and sad. [45]

Two years later the husband has become azoospermic, that is sterile, and the couple has been going on a personal path of marital growth. The chart expresses the current situation and shows delayed ovulation in which the hyperprolactinemia is "iatrogenic", i.e. it is due to psychotropic drugs, which are able to induce a pattern paradoxically very similar to that of the lactating woman. (Figure 24)

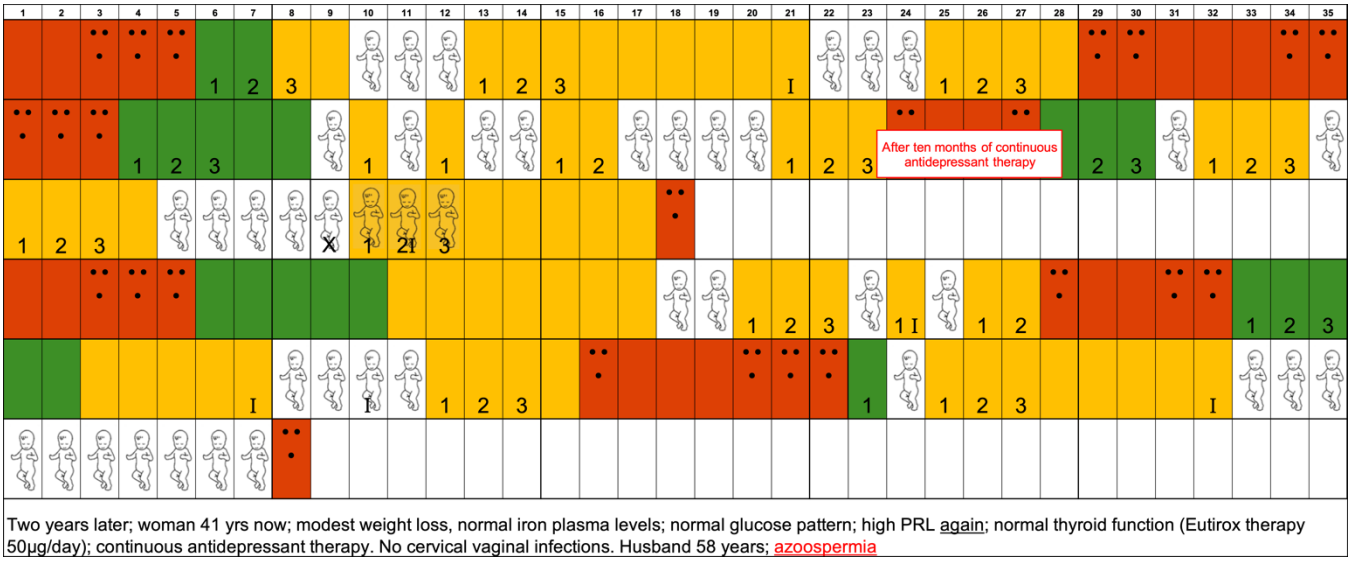

Figure 24. Very rare ovulations in iatrogenic hyperprolactinemia due to antidepressants.

The couple continues to record the Billings Ovulation Method® not only to monitor the effects of treatment on the woman's cycle, but because they are finding in this activity a privileged moment of sharing and of marital intimacy. The openness to life and the rediscovery of the marital relationship are as equally

important as the conception and show that, even in couples defined as infertile, it is always possible to live an authentic conjugal fecundity.

These stories are also useful for physicians because they propose the importance of a correct differential diagnosis of the causes of hyperprolactinemia, which may be physiological, such as during breastfeeding, or pathological.

The PRL influences fertility by acting at three different levels: the hypothalamic-pituitary axis, where the secretion of gonadotropins FSH and LH can be impaired, through the alteration of pulsatile GnRH hypothalamic; at ovarian level, where it modifies the activity of the receptors for FSH and LH, either directly, or indirectly through the increase of adrenal androgens (adrenal level). [46]

Among the pathological forms, the role of hypothyroidism is much underestimated, since the same scientific literature says, 30 years later, that the problem has still not been solved. [47, 48]

It is well known that thyroid dysfunctions, mainly hypothyroidism, adversely affect fertility, also causing the increase of the PRL. The way in which PRL and Thyroid interact, is regarding the factors that regulate the production of PRL. PRL is usually under a prevailing inhibitory control by dopamine (DA); Estrogen can instead stimulate production (for example, it is not an uncommon experience to find galactorrhoea in women taking the pill). For this reason, the best time in the cycle to perform the assay of the basal PRL is the 2nd-3rd day, when estrogens are physiologically at a minimum. (Figure 25)

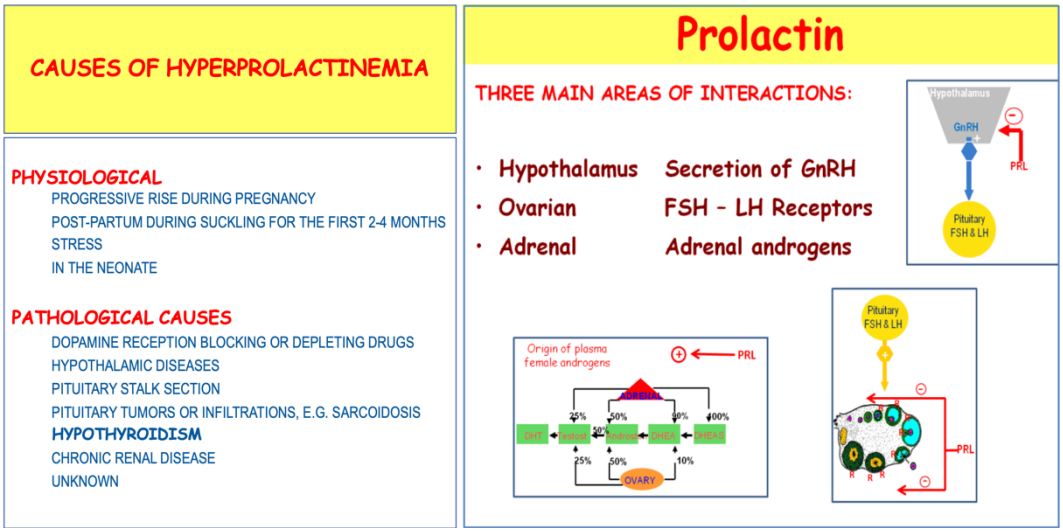

Figure 145. Hyperprolactinemia affects fertility by acting though three main areas. Hypothyroidism can cause secondary hyperprolactinemia, but it seems often an underestimated problem.

The TRH (Thyrotropin Releasing Hormone), the hormone stimulating the hypothalamic pituitary TSH secretion, is not a physiological PRF (Prolactin Releasing Factor). For example, the suckling by breastfeeding is a physiological stimulus to the release of prolactin but is not followed by a contemporary TSH secretion. The only pathological situation in which there has been a simultaneous increase in both TSH and PRL is hypothyroidism. [49,50]

Chronic hypothyroidism causes hypertrophy of the pituitary TSH cells, with increase of the gland. The mass effect, associated with hyperprolactinemia can simulate a Prolactinoma. For these reasons all patients with high PRL should be studied for thyroid function. [51] (Figure 26)

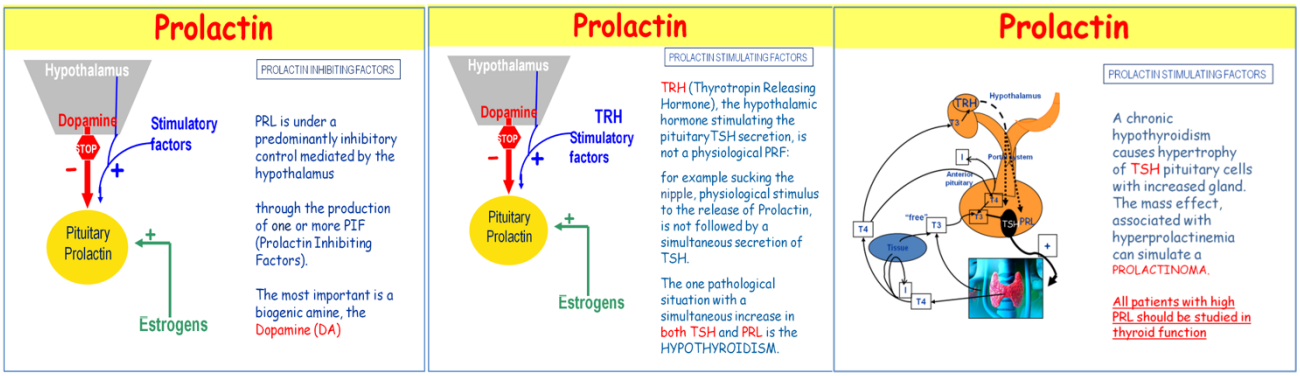

Figure 26. Hypothyroidism and increased PRL. A correct differential diagnosis is important for the purposes of an adequate therapy.

An increased PRL and the negative effects of hypothyroidism can occur even when the thyroid gland is impaired but is still able to produce hormone levels within the normal range: we can say in this case of "subclinical hypothyroidism". [52,53]

Since the thyroid hormone levels may be normal, it is indicated to use the TRH test to make a diagnosis. The test reveals a latent situation when the Delta TSH exceeds 15 µU/ml at 30' and can be performed at any time in the cycle and allows an evaluation of the opportunity to start a thyroid replacement therapy, which will lead to normalizing the PRL value. Where it is difficult to perform this test, some simple indications of good clinical practice can be applied. Combining data obtained from the interview with the patient, the ultrasound examination, and assessing in a competent way the dosages of the basal hormones, can allow for a diagnosis. For example, by noting a preferential synthesis of FT3 and/or the TSH at the upper limits of the range (if this is very narrow. e.g., 0.5 - 3.20 - TSH value equal to 2.7 is diagnostic), these all are signs of impaired thyroid activity. (Figure 27)

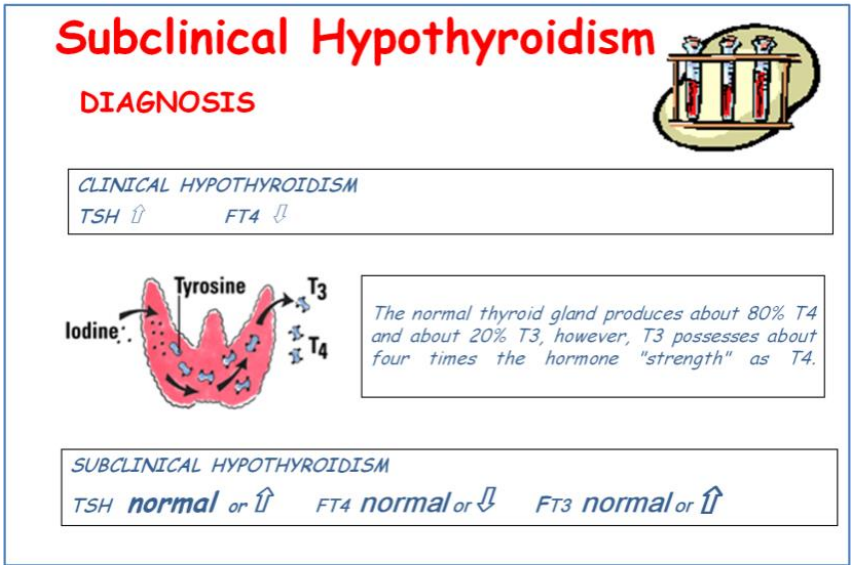

Figure 157. If a subclinical hypothyroidism presents hormonal values in the normal range, the TRH test is indicated to reveal that it is there.

The topic of the diagnosis of endocrine extra-ovarian dysfunctions cannot be exhausted in these few notes but offers a proposal of reflection on the role of doctors and scientists, who examine the women's registered cycles. Professor Brown has fully realized the validity of the Billings Ovulation Method® and, according to the great humility of the true scientists, invites women to carefully follow the Method for these reasons:

"Dear ladies, you're ahead: as scientists we can only follow you, by checking the validity of your observations. We don't possess any absolute measurement of ovulation or fertility. We talk about statistics and failure rates. We draw complicated and interesting diagrams to show how the nervous centres affect reproductive processes. As women, you base on the Method your lives, your hopes, your children, your marriage. You know that emotional factors can affect your charting, and that your records tell the story of your life. The man must be humble in front of this. I have learned that discrepancies between your observations and our results were often caused by errors of calculation from us. Dear ladies, hold on, continue to observe and to improve, to keep accurate charting and don't be misled, consenting to the seemingly superior knowledge of man. Prof James B. Brown"

The Billings Ovulation Method® has always proposed to all people the harmony and integral perspective of being fecund in love. The commitment to education, especially important for new generations, contemplates the corporeality, as the interior and spiritual dimension, recognizing and valuing the specificity and beauty inherent in human nature.

Acknowledgements

The wonderful scientists, inventors and promoters of the Billings Ovulation Method® who were marvellous masters of life and science; the WOOMB Directors who are carrying this work on in the world; the team of the Centre/ISI of Rome with the Director Riccardo Marana; Carmen Manno for the contribution to English translation. Finally, all the couples and teachers of the Billings Ovulation Method®, for their generous and silent work, that makes them witnesses of love, every time they help a couple in the personal conquest of this precious treasure that is the Billings Ovulation Method®.

References

1. Billings EL, Brown JB, Billings JJ, Burger HJ. Symptoms and hormonal changes accompanying ovulation. Lancet 1972; 1(7745): 282-284.
2. Billings JJ. The validation of the Billings Ovulation Method by laboratory research and field trials. Acta Eur Fertil 1991; 22(1): 9-15.
3. Task Force on methods of the determination of the fertile period. A prospective multicentre trial of the ovulation method of natural family planning. II. The effectiveness phase. Fertil Steril 1981; 36:591-8.
4. Indian Council of medical research: Field trials of Billings Ovulation Method of Natural Family Planning. Contraception 1996; 53: 69-74.
5. Xu JX, Yan JH, Fan DZ, Zhang DW. Billings natural family planning in Shanghai, China. Adv Contracept 1994; 10(3):195.
6. Cappella A. Secondo natura – Il Metodo Billings. Torino, BBE, 1985
7. Giovanni Paolo II. Uomo e donna: Catechesi sull'amore umano. LEV Città Nuova, Roma 1985, XV, 77.

8. Brown JB. Scientific basis of the Ovulation Method. In Billings JJ et Al.: The Billings Atlas of the Ovulation Method. Appendix 2, p. 95-101. 5th ed. 1989. Ovulation Method Research & Reference Centre of Australia – Melbourne.
9. Odeblad E. The cervix, the vagina and fertility. In Billings JJ et Al.: The Billings Atlas of the Ovulation Method. Appendix 1, p. 85-94. 5th ed. 1989. Ovulation Method Research & Reference Centre of Australia – Melbourne.
10. Brown JB. Timing of ovulation. Med J Austr, 1977 Dec 3;2(23):780-3.
11. Brown JB, Blackwell LF, Holmes J, Smyth K. New assays for identifying the fertile period. Suppl Int J Gynecol & Obstet. 1989; 1:111-22.
12. Blackwell LF, Brown JB, Cooke D. Definition of the potentially fertile period from urinary steroid excretion rates. Part II. A threshold value for pregnanediol glucuronide as a marker for the end of the potentially fertile period in the human menstrual cycle. Steroids. 1998;63(1): 5-13.
13. Blackwell LF, Brown JB, Vigil P, Gross B, Sufi S, d' Arcangues C. Hormonal monitoring of ovarian activity using the Ovarian Monitor, part I. Validation of home and laboratory results obtained during ovulatory cycles comparison with radioimmunoassay. Steroids 2003; 68(5):465-76.
14. Blackwell LF, Vigil P, Cooke D, d'Arcangues C, Brown JB. Monitoring of ovarian activity by daily measurement of urinary excretion rates of oestrone glucuronide and pregnanediol glucuronide using the Ovarian Monitor, Part III: variability of normal menstrual cycle profiles. Hum Reprod. 2013 Dec; 28(12):3306-15. doi: 10.1093/humrep/det389.
15. Saporosi A, Squintani MC, Pompa G, Cappella A. Recent advances on scientific research in natural family planning. In: Women's Health Issue, AG Spagnolo & G Gambino, Ed. Universo, Roma, 2003, pp331-35
16. ESHRE Capri Workshop Group. Mono-ovulatory cycles: a key goal in pro fertility programs. Human Reprod Update,2003;9(3): pp263-74
17. Gougeon A: Dynamics of follicular growth in the human: A model from preliminary results. Hum Reprod,1986. 1: 81,
18. Erickson GF: Follicle Growth and Development. In: Williams RE (ed) Williams Textbook of Endocrinology, 2016,13th ed, Vol 5, Chap 12.
19. Monniaux D, Clèment F, Dalbiés-Tran R, Estienne A, Fabre S, Mansanet C and Monget P. The ovarian reserve of primordial follicles and the dynamic reserve of antral growing follicles: what is the link? Biol Reprod, 2014; 90(4):85, 1-11.
20. Baerwald AR, Adams GP and Pierson RA. A new model for ovarian follicular development during the human menstrual cycle. Fertil Steril 2003 Jul; 80(1):116-22.
21. Thornton SJ, Peperell RJ, Brown JB. Home monitoring of gonadotropin ovulation induction using the Ovarian Monitorr. Fertil Steril 1990 Dec; 54(6):107.
22. Brown JB. Types of ovarian activity in women and their significance: the continuum (a reinterpretation of early findings). Human Reproduction Update, 2010 Oct,1–18, doi:10.1093/humupd/dmq040.
23. Brown JB. Hormonal basis of natural fertility regulation. In Scienza ed etica per una procreazione responsabile, Libreria Cortina Verona, pp 31-48, 2008
24. Pallone SR and Bergus GR. Fertility awareness-based methods: another option for family planning. J Am Board Fam Med 2009; 22:147-15.
25. J Bigelow, D Dunson, J Stanford, R Ecochard, C Gnoth, B Colombo. Mucus observation in the fertile window: a better predictor of conception than timing of intercourse. Hum Reprod 2004; 19:889-92.
26. Ecochard R, Duterque O, Leiva R, Bouchard T, Vigil P. Self-identification of the clinical fertile window and the ovulation period. Fertil Steril. 2015 May; 103(5):1319-25.
27. Scarpa B, Dunson DB, Giacchi E. Bayesian selection of optimal rules for timing intercourse to conceive by using calendar and mucus. Fertil Steril. 2007 Oct; 88(4):915-24.
28. Cappella A, Saporosi A. Regulaciòn natural de la fertilidad: el Monitor Ovarico de Brown. Medicina y Etica: Revista Internacional de Bioetica, Deontologia y Etica Medica, Universidad Anàhuac, Mexico, 2000. Vol. XI, 1:93-104.
29. Saporosi A, Cappella A and Brown JB. Update on ovulation and fertility monitoring by cervical mucus symptom and urinary hormone assay. Int J Gynecol Obst, suppl 1, 2000 Sept, p36.
31. Saporosi A, Giacchi E, Squintani MC, Menini E, Cappella A, Brown JB. Reliability of modern technology as aid to natural family planning for spacing pregnancy. Int J Gynecol Obst, suppl 1, Sept 2000, p. 97.

32. Giacchi E, Saporosi A, Castellucci P, Di Donna V, Festa R, Mancini A. The Billings Ovulation MethodTM as a useful tool in diagnostic evaluation of endocrine and cervical pathologies affecting fertility. Int J Gynecol Obst 2009 Oct, O575.
33. ISTAT, Italian Institut of Statistics, Annual report 2015 - The state of the Nation; Health statistics: Pregnancy, childbirth and breastfeeding in Italy. Available at www.istat.it/en/archive/annual+report.
34. Borrie WD. Fertility, infertility and generation replacement. Clin Reprod Fertil 1986 Feb;4(1):55-64.
35. Broekmans FJ, Knauff EA, Velde ER, Macklon NS, Fauser BC. Female reproductive ageing: current knowledge and future trends. Trends Endocrinol Metab 2007 Mar;18(2):58-65.
36. Jayaprakasan K, Deb S, Batcha M, Hopkisson J, Johnson I, Campbell B, Raine-Fenning N. The cohort of antral follicles measuring 2-6 mm reflects the quantitative status of ovarian reserve as assessed by serum levels of anti-Müllerian hormone and response to controlled ovarian stimulation. Fertil Steril 2010 Oct;94(5):1775-81. doi: 10.1016/j.fertnstert.2009.10.022.
37. Broekmans FJM, De Ziegler D, Howles CM, Gougeon A, Trew G, Olivennes F. The antral follicle count: practical recommendations for better standardization. Fertil Steril 2010;94(3):1044–1051. doi: 10.1016/j. fertnstert.2009.04.040.
38. Tremellen K P, Kolo M, Gilmore A, Lekamge DN. Anti-müllerian hormone as a marker of ovarian reserve. Austr NZ J Obst Gynaecol 2005;45(1):20–24. doi: 10.1111/j.1479-828X.2005.00332.x.
39. Saporosi A, Mancini A, Menini E, De Marinis L, Cappella A. Urine hormone assays to evaluate fertility and luteal function in 113 cycles. Gynecol Endocrinol 2000 Dec, 14 (Suppl. 2): p 56.
40. Saporosi A. The mucus symptom in abnormal cycles. International Conference “Procreation today: the challenge of natural fertility regulation”. Catholic University of the Sacred Heart - Rome, 15th – 16th nov, 2014.
41. Hassan MAM and Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril 2004 Feb; 81(2):384-392.
42. Saporosi A, Giuliani G, Giacchi E, Di Segni C, Mancini A, Marana R. Human sexuality, fertility and lifestyles: Billings Ovulation Method® contribution in clinical protocols for infertility treatment. XVI World Congress on Human Reproduction, Berlin, Germany, 2015, 12th–21st March, Available at: http://gest.btcongress. it/viewAbstractPdf.php?id=3445.
43. ISTAT Italian Institute of Statistics. Annual report 2008 - The state of the Nation; Daily life. Available at www.istat.it/en/archive/annual+report.
44. Billings EL, Billings Ovulation Method® and Achieving Pregnancy. In: Billings Atlas of the Ovulation Method: the mucus patterns of fertility and infertility, by Billings EL, Billings JJ and Catarinich M, Fifth Edition 1989, pp 51-55. revised by Dr E L Billings 2009.
45. Elliott PJ, Nature and Grace and the Billings Ovulation Method®, International Billings Ovulation Method® Conference, Melbourne, May 1st 2009. Available at: http://www.woomb.org/philosophy/nature-and- grace-and-the-billings-ovulation method%e2%84%a2.html
46. Billings EL, Corkill M, Marshell M. The cultural value of Natural Family Planning: International Conference for the 40th Anniversary of the Encyclical Letter Humanae Vitae, Pontifical Lateran University, Rome, 2008 May.
47. Molitch ME. Prolactin in human reproduction. In: Yen & Jaffe’s Reproductive Endocrinology. 6th Ed, 2009, pp 57-78.
48. Barnes BO and Galton L. Hypothyroidism. The Unsuspected Illness, Harper Collins Ed. New York, 1976.
49. Starr M. Hypothyroidism Type 2, The Hidden Epidemic, 2006, M Starr Trust, Columbia Missouri. Available at: http://www.doctormarkstarr.com/hypothyroidism.
50. Fritz M, Speroff L. Reproduction and the thyroid. In: Clinical Gynaecology, Endocrinology and Infertility, Lippincott Williams & Wilkins, 8th Ed, 2011, pp 885.
51. Bulen SE. Physiology and pathology of the female reproductive axis. In: Williams Textbook of Endocrinology, 12th Ed, 2011, pp 581-660.
52. Han L, Wang J, Shu K, Lei T. Pituitary tumorous hyperplasia due to primary hypothyroidism. Acta Neurochir 2012 Aug;154(8):1489-92.
53. Salvatore D, Davies TF, Schlumberger MJ, HAy ID, Larsen PR. Thyroid physiology and evaluation of patients with thyroid disorders. In: William Textbook of Endocrinology, 12th Ed, 2011, pp 327-361.
54. Hekimsoy Z, Kafesciler S, Guclu F and Ozmen B. The prevalence of hyperprolactinemia in overt and sub-clinical Hypothyroidism. Endocr J 2010, 57(12), 1011-1015.