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Fertile Window Biomarkers: Update in Natural Cycles and Fertility Awarness

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Abstract:

There is currently sufficient scientific evidence that children conceived by artificial reproduction technique (ART) have a higher relative risk of having a health-related problem, in the short, medium or long term. These data have been observed compared to that of children conceived through natural cycles, or cycles in which restorative and resortive measures have been applied in human reproduction, preserving the dignity of the person. This article reviews the main existing biomarkers of the fertile window within a process of development of an oocyte through natural cycles, or monofollicular stimulation that could culminate in a viable, intrauterine embryo, with a father and a mother as custodial parents. Among the problems avoided with this type of natural cycles are some types of congenital anatomic anomalies, perinatal complications, such as preterm delivery, low or very low birth weight, or intrauterine growth retardation, and some genetic syndromes. .Cardiovascular, metabolic problems, respiratory diseases, some oncological processes and cerebral palsy are avoided. Other negative scientific evidences are the epigenetic consequences derived from the side effects of ART, for this reason conflicts between desiring or having a child are avoided at the expense of a greater risk to their health, due to the aforementioned risks, in addition to the eventual absence of parents necessary to ensure the care and custody of the children, which would be created through TRA protocols.

Discussion:

The main objective of this article is to review some fundamental contributions of the fertile window from relevant clinical studies of it and then to integrate different concepts that relate biological signals and markers, which have allowed identifying the phases of the menstrual cycles and their clinical applications. For this, some physiological concepts related to ovulation, secretion and metabolism of follicle stimulating hormone are reviewed, together with the clinical, biographical and biochemical study of follicular development. The ovary has a follicular cohort of antral follicles sensitive to a certain concentration of FSH, for a certain period of time. In such a way that in the face of an increase in FSH, it is possible to rescue a certain follicular pool for its entry into the process of selection, recruitment and follicular maturity. What is known as the FSH threshold, that is, the period of influence under which a pool of follicles are likely to be rescued. Once the follicular rescue has taken place, the dominant follicle presents greater sensitivity to FSH, estrogen receptors increase, granulosa cells and their aromatization increase, to achieve a follicle follicular dominance. A practical approach is carried out to apply the concepts related to the fertile window, both in the recognition of fertility in menstrual cycles, and in the contributions of clinical biomarkers, and in the restoration of pathological cycles in patients with fertility problems.

The cyclicality and regularity of menstrual cycles is determined by the interaction of the hormones of the hypothalamic-pituitary-gonadal axis. This coordinated interaction is achieved by pulsatile release of hypothalamic gonadotropins (GNRH) , in conjunction with the dynamics of follicular development and FSH metabolism. The ovary has a follicular cohort every month with sensitive antral follicles.

One degree of concentration determins the follicle stimulating hormone (FSH) (1). The 1 and 4 day, preantral follicles are sensitive to an increase in serum FSH concentration over time, and to its own threshold. At this stage, the antral follicle requires the presence of two essential and fundamental physiological situations to be rescued; One is the need to have receptors sensitive to the action of FSH, in order to be rescued from the follicular pool, and the second is that adequate aromatization occurs in the antral follicle (2). The increase in estrogens is decisive for stimulating FSH receptors in the preantral follicle for about 5-12 days, which requires a significant increase in the number of stromal cells. This multiplier game between receptors and stomach cells is known as the snowball-like-effect, which in turn is enhanced by various signals, including redistribution of peri-follicular flow, mediated by the vascular endothelial growth factor (VEGF). This factor increases the supply of vascular blood to the follicle. In this way, a proper physiological state of cyclical self-determination is achieved under normal conditions of the menstrual cycle. The final stage of the dominant follicle is usually evident with a pre-ovulatory follicle of around 18 mm, which finishes maturing under the action of luteinizing hormone (LH). This hormone is crucial for the final re-shaping phase of granulosa cells, continues the aromatization of androgens from the theca cells, and produces the LH surge necessary for ovulation to occur (1-2). Finally, the dominant follicle increases the secretion of inhibin, which prevents the secretion of FSH, and the reentry of new follicles, in such a way that the small follicles (FSH dependent), cannot sufficiently acquire aromatization and become small androgenic and atretic . This natural model of mono-follicular growth can be interrupted by external mechanisms, or some endogenous endocrinological alteration (3).

Conclusion: Summary and practical applications

Currently it is possible to detect the period of greatest fertility around day -6, before ovulation, until the first day after ovulation, this time interval being recognized as the clinical window of fertility physiology. The estimated day of ovulation has been used to retrospectively determine changes from a period of infertility to a state of fertility . This methodology has made it possible define the fertility window to be used in clinical practice , and to detect the period fertile by different well-documented methods. Currently it is possible to detect through clinical parameters the phase change from infertile days to the days of greatest fertility within the menstrual cycle. The interval of the clinical fertile window is usually longer than the physiological window . The changes observed at the vulvar level of cervical secretion can also be used to identify the beginning of the fertility window and the end of the fertile interval in subfertile patients. This method has a well-established biological justification,, because the type of estrogen-dependent cervical secretion increases about 5-6 days before the day of ovulation. Estrogenic- type cervical discharge serves not

only as an indicator of fertile days, but also allows establishing the window of maximum fertility by estimating clinical parameters with the most fertile characteristics of cervical mucus, or in conjunction with ultrasound of the window of ovulation. It can also predict non-fertile secretion due to the absence of sufficient levels of secretion with estrogenic characteristics . A good connection has been seen among the opening and close signals of the fertile period, cycles of subfertile women . In subfertile patients promoting preconception health (ie, weight loss, smoking cessation) , low cost fertility technologies that delimit a point of care (POC) may be associated with clinical parameters, through the means of over-the-counter ovulation prediction kits to increase the chances of spontaneous pregnancy . The correlation between serum and urinary measurements of sex hormones from day -6 before ovulation to day 1+ after ovulation is currently well documented ,which allows the application of new technologies.