

# Multiple ovulations between ovarian stimulation treatment and primary ovarian insufficiency

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## ABSTRACT

The release of several oocytes during the same menstrual cycle can occur both physiologically and iatrogenic, following ovarian stimulation treatments. Ovarian induction can be achieved either by mild stimulation, in the case of anovulatory or dysovulatory patients, or by controlled ovarian hyperstimulation, to obtain a large number of follicles in the In Vitro Fertilization procedure. At this time, the ideal ovarian stimulation treatment is to suppress the pituitary release of gonadotrophin-releasing hormone (GnRH), a co-opted regimen with high doses of exogenous follicle-stimulating hormone (FSH). The physiological process of multiple ovulations can lead to superfertilization (SF). SF is a biological process by which two eggs are fertilized successively, at intervals of a few days apart, both eggs coming from the same ovulation. Among the factors that can lead to superfertilization are mentioned: family history of dizygotic pregnancies (DZ), increased parity, advanced age, high stature of women, a high weight index, the use of oral contraceptives and folic acid. The premenopausal period is characterized by elevated levels of FSH and a low ovarian reserve, both conditions contributing to the development of multiple follicular and DZ pregnancies.

**Keywords:** ovarian stimulation, dizygotic pregnancy, multiple follicles, premenopausal period, FSH level, ovarian failure

## INTRODUCTION

Ovulation is the physiological disruption of ovarian tissue and the release of the oocyte whose viability for fertilization is the next 12-24 hours. The process occurs after selecting and differentiating a single ovarian follicle and is based on the interaction between the hypothalamic-pituitary axis and the ovaries. After the follicle destined to evolve is selected, it shows marked changes in its steroidogenic activity (1).

The release of several oocytes during the same menstrual cycle can occur both physiologically and

iatrogenic, following ovarian stimulation treatments (2). Nowadays, ovulation induction is a major treatment for many causes of infertility. This procedure should be closely monitored to prevent complications, multiple pregnancies, and ovarian hyperstimulation syndrome. Ovarian induction can be achieved either by mild stimulation, in the case of anovulatory or dysovulatory patients, or by controlled ovarian hyperstimulation, in order to obtain a large number of follicles in the In Vitro Fertilization procedure (3).

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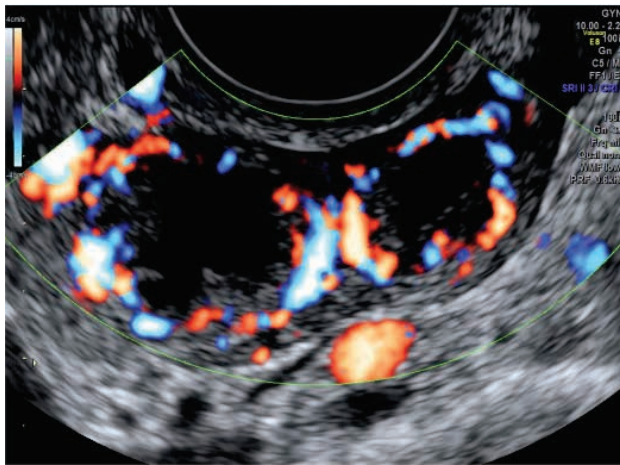
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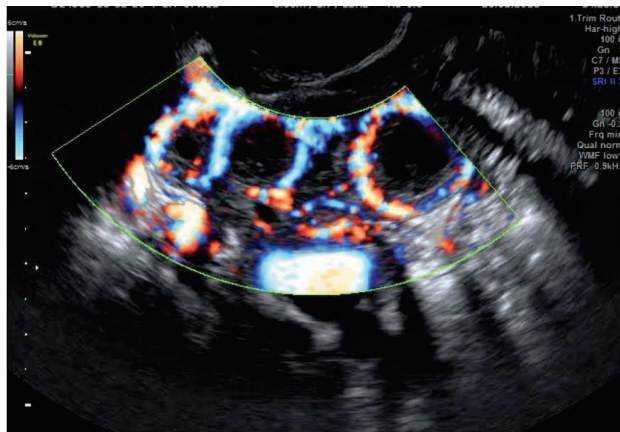
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The physiological process of multiple ovulations can lead to superfertilization (SF). SF is a biological process by which two eggs are fertilized successively, at intervals of a few days apart, both eggs coming from the same ovulation. The incidence of double ovulation remains unknown. Multiple ovulations can be synchronous or sequential in the same cycle, which makes polyzygosity preceded by multiple fertilization following one or more inseminations, natural or artificial. Thus, superfertilization is a phenomenon that leads to the appearance of zygotes with identical or different conceptual ages (4,5).

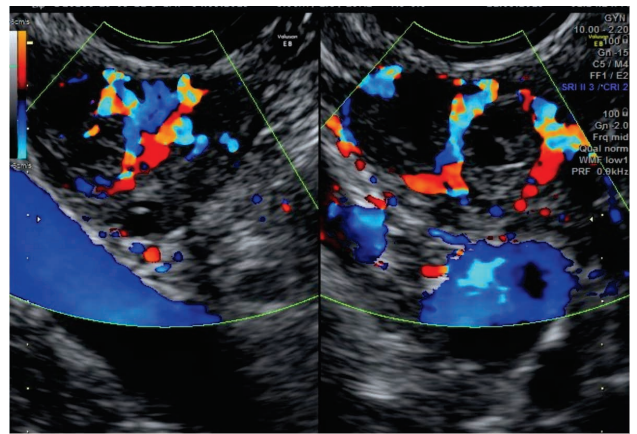
The conceptualization of this article is based on the clinical observation that regardless of the patients' age in whom the ultrasound shows a low follicular reserve, regardless of whether they are in preclimax or before premature ovarian failure installation, spontaneous multiple ovulation appears on the ovaries with a very small number of follicles. Our experience consists in 12 cases of patients (Figures 1-5) without clinical complaining, presented for a routine transvaginal ultrasound examination, without any familial history of twin pregnancies.



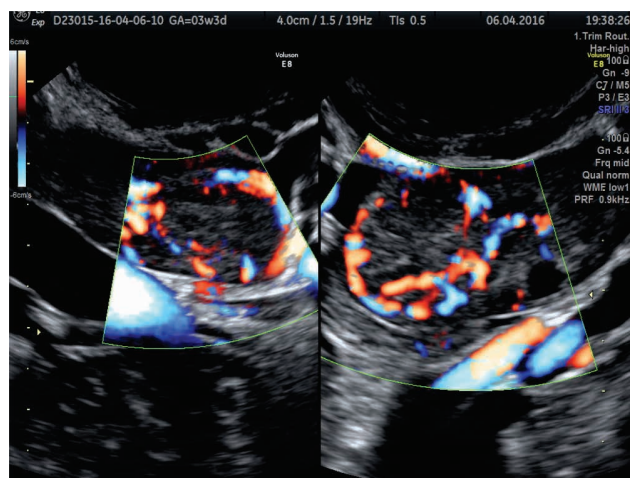
**FIGURE 1.** Double follicular maturation in the same ovarian cycle



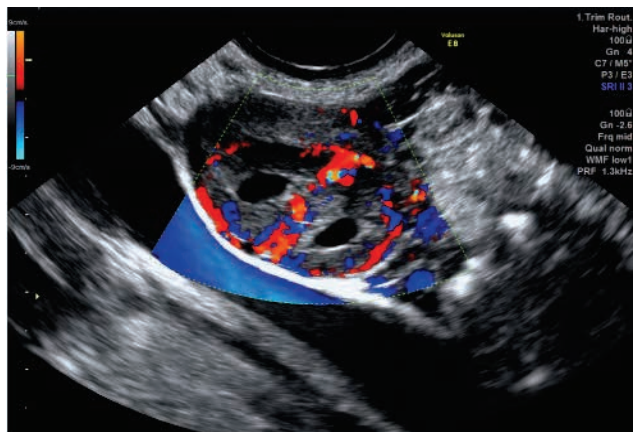
**FIGURE 2.** Spontaneous development of three ovarian follicles without exogenous hyperstimulation



**FIGURE 3.** Spontaneous development of three ovarian follicles on both ovaries



**FIGURE 4.** Bilateral spontaneous ovulation in singleton pregnancy



**FIGURE 5.** Spontaneous double ovulation on the same ovary

The aim of this article is to represent a pilot study to further evaluate the hormonal context in which multiple ovulation occurs. Figures 1-5 are included in the personal collection of Roxana Bohiltea.

## DISCUSSION

The biochemical evaluation of the hormonal status of women with primary ovarian insufficiency

includes FSH (follicle-stimulating hormone), E2 (estradiol), PRL (prolactin) and TSH (thyroid-stimulating hormone) testing. Anti-Müllerian hormone (AMH) can be useful to determine the ovarian reserve. Most important, if the patient has regular menses, FSH should be measured in the 3rd day of a menstrual cycle, if not it can be measured randomly (6). Primary ovarian insufficiency is characterized by a low serum value of AMH with an increased serum value of FSH.

The differential diagnosis of primary ovarian failure should be made with treatments that could alter the ovarian tissue (chemotherapy, radiotherapy, history of ovarian surgery), primary adrenal insufficiency (7), autoimmune disorders (8), fragile X syndrome cases in the family (9), family history of primary ovarian insufficiency (10) as well as with Perrault syndrome (11).

Ovulatory induction and superovulation are among the most widely used infertility treatments in anovulatory women. Medication for this purpose is based on the administration of exogenous gonadotropins or the administration of clomiphene citrate to stimulate endogenous FSH (12). Thus, following these processes, a multiple follicular development is obtained (13), what is considered to be a negative effect, taking into account the risks associated with multiple pregnancies (14). At this time, the ideal ovarian stimulation treatment is to suppress the pituitary release of gonadotrophin-releasing hormone (GnRH), a co-opted regimen with high doses of exogenous follicle-stimulating hormone (FSH) (15).

The exact incidence of dizygotic pregnancy (DZ) is not known at this time, varying in some studies from 3-5/1000 (16) to 13/1000. The spontaneous development of DZ pregnancies depends very much on the characteristics of the mother; studies show that mothers with a family history of DZ pregnancies, increased parity and advanced age are prone to have DZ pregnancies (17). Among the factors that can lead to the development of multiple follicles in the same menstrual cycle, and also the incidence of DZ pregnancies, there are the following: high stature of women, a high weight index, the use of oral contraceptives and folic acid. Genetic analysis is beginning to identify mutations in genes that are significantly more common in mothers with DZ twins, and which may underlie this twinning (16,17). Al-

though it seems a paradoxical phenomenon, advanced maternal age is associated with a higher rate of development of DZ pregnancies (16-19), over 2% for mothers aged over 35 compared to <1% for mothers under 25 and, appearing to be based on an endocrine mechanism. The premenopausal period is characterized by elevated levels of FSH in the early follicular phase, and most women go through a period of occult or incipient ovarian failure (18).

Although curious, both conditions, respectively the low ovarian reserve and the increased level of FSH together contribute to the development of multiple follicular and DZ pregnancies (18). During reproductive life, FSH levels leading to monofollicular growth are relatively constant, with no substantial changes from threshold, due to ovarian feedback mechanisms (18,20). With age, the effectiveness of ovarian feedback compensatory mechanisms decreases, leading to elevated FSH levels (21). In general, this does not lead to the development of multiple dizygotic pregnancies, as the phenomenon is flattened by low follicular reserve. However, by chance, under the action of high levels of FSH, two or more high-quality follicles begin to grow and ovulate at the same time, thus being prepared for fertilization and nesting (18).

## CONCLUSIONS

The maturation of several ovarian follicles during the same ovarian cycle is a complex phenomenon, but with insufficient information on the impact. It can occur both iatrogenic, after ovarian stimulation treatment and spontaneously. The spontaneous appearance of multiple ovulations depends on several factors, the advanced maternal age being one of them. Although it seems a paradoxical phenomenon, double ovulation and dizygotic pregnancy has an increased incidence in premenopausal women, an event explained by a decrease in the ovarian hormone's ability to regulate hormones, which leads to an increase in FSH levels.

It should be investigated the context of multiple ovulations' appearance in women before the age of 40, as it could possible represent an early sign of primary ovarian failure, in order to counsel women without offsprings to complete their family as quickly as possible.

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