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REVIEW

Ovarian function during hormonal contraception assessed by endocrine and sonographic markers: a systematic review

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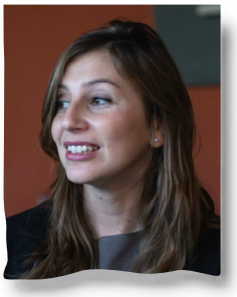

Dr Stella D'Arpe graduated from the Medical School at the University of Rome 'Sapienza' in 2007. In 2014 she completed her gynaecological and obstetrical residency training at Rome University Hospital. Currently, she is completing her PhD thesis on the clinical, endocrine and sexual impact of hormonal contraceptives comparing different dose of steroids and administration modes at Rome University Hospital.

Abstract This systematic review focuses on the literature evidence for residual ovarian function during treatment with hormonal contraceptives. We reviewed all papers which assessed residual ovarian activity during hormonal contraceptive use, using endocrine markers such as serum anti-Müllerian hormone (AMH) concentrations, FSH, LH, oestradiol, progesterone and sonographic markers such as antral follicle count (AFC), ovarian volume and vascular indices. We considered every type (oestroprogestin or only progestin) and dosage of hormonal contraceptive and every mode of administration (oral, vaginal ring, implant, transdermal patch). We performed an electronic database search for papers published from 1 January 1990 until 30 November 2015 using PubMed and MEDLINE. We pre-selected 113 studies and judged 48 studies suitable for the review. Most studies showed that follicular development continues during treatment with hormonal contraceptives, and that during treatment there is a reduction in serum concentrations of FSH, LH and oestradiol, and also a reduction in endometrial thickness, ovarian volume and the number and size of antral follicles. The ovarian reserve parameters, namely AFC and ovarian volume, are lower among users than among non-users of hormonal contraception; regarding the effect of hormonal contraception on AMH, there are still controversies in the literature.

KEYWORDS: follicular development, hormonal contraception, hormone-free interval, ovarian activity, ovarian function

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Introduction

The most important effect of hormonal contraception is the inhibition of hypothalamo-pituitary axis causing a decrease in FSH and LH, leading to the suppression of follicular activity and ovulation. In the last 50 years, the composition of hormonal contraceptives has undergone several modifications in order to reduce as much as possible the side effects, and to increase the compliance of women, while preserving contraceptive efficacy. Scientific literature shows that reducing the dose of oestrogen of combined contraceptives, to minimize its adverse effects, is associated with a decrease in pituitary gonadotrophin secretion, particularly during the hormone-free interval (HFI) or following missed doses, resulting in greater follicular development (Baerwald and Pierson, 2004). In this regard, several studies have evaluated the residual ovarian function during treatment with hormonal contraceptives, comparing different doses of steroids, duration of the HFI, and administration schemes. Many authors tried to study the ovarian function using endocrine markers like serum anti-Müllerian hormone (AMH) concentrations, FSH, LH, oestradiol, progesterone and sonographic markers such as antral follicle count (AFC), ovarian volume and vascular indices. The aim of this review is to give a complete evaluation of residual ovarian activity during hormonal contraceptive use.

Materials and methods

The present systematic review included all scientific articles which assessed residual ovarian activity during hormonal contraceptive use. All articles reporting ovarian activity as evaluated with either sonographic parameters or biochemical parameters were included. Studies were excluded if reporting only biochemical parameters. Every type and dosage (oestroprogestin [EP] or only progestin) of hormonal contraceptive and every mode of administration (oral, vaginal ring, implant, transdermal patch) were considered.

Included studies were randomized clinical trials, prospective controlled studies, prospective cohort studies or retrospective studies with a sample ≥30 patients in good health. Studies about women in breastfeeding or overweight were excluded. Only articles written in English were included.

An electronic database search was performed using PubMed and MEDLINE for the identification of articles published from 1 January 1990 to 30 November 2015, using the combination of the following search terms: contraceptives, hormonal contraceptives, contraception, hormonal contraception, steroid contraception, oral contraception, oestroprogestins, follicle, follicle development, follicular development, hormone-free interval, ovarian activity, ovarian function, AMH, LH, FSH, follicle cysts, ovarian cysts, ovulation, ultrasound. Three investigators independently conducted this search. After the search, all relevant studies were retrieved based on the title and the abstract content, and their reference lists were checked manually to identify additional potential studies. The full text of the identified papers was analysed independently by three investigators with the purpose of determining whether or not to include the article in the systematic review. In cases of incomplete data, studies were excluded. In cases of disagreement in the review process, consensus was achieved through the involvement of other investigators.

One hundred and thirteen studies were pre-selected after the electronic search based on the article title and abstract, and after a manual search of the reference lists of the full articles. After reading of the full text, a total of 67 articles were excluded. A total of 46 studies were therefore judged suitable for the review (**Figure 1**).

Ovarian function during combined contraceptive use

It has been shown that oestrogens and progestins at the concentrations above physiological level, produce a negative feedback effect on the hypothalamo-pituitary axis (Wan et al., 1981). Presumably reduced gonadotrophin-releasing hormone (GnRH), FSH and LH concentrations inhibit ovarian follicular growth and consequently suppress ovulation and conception. The progestins have been shown to prevent the LH surge and ovulation (Barnhart et al., 1997; Tafurt et al., 1980). The oestrogens are believed to suppress the development of preantral and medium-sized antral follicles in primates (Koering et al., 1991, 1994), presumably through suppression of FSH secretion. Moreover, oestrogens have the function of improving satisfaction of patients avoiding irregular bleeding patterns. However, during the use of EP, residual follicular activity has been shown to persist. In women using a combined oral contraceptive (COC), the degree of follicular activity seems to depend on the dose of ethinyl oestradiol (EE) rather than on the dose and type of progestin. (Fauser and Van Heusden, 1997; Spellacy et al., 1980). In fact, during low EE dose formulations use, greater numbers and bigger diameter of follicles are observed (Teichmann et al., 1995). Therefore, the decrease of oestrogen dose in COC could reduce the degree of hypothalamo-pituitary ovarian suppression especially after missed doses, or during HFI. Indeed, in women using COC, follicular growth appears to take place more frequently during HFI, where there is a loss of endocrine suppression (Rabe et al., 1997).

Three prospective studies examined ovarian function in women using a single formulation of COC (Deb et al., 2012; Hoogland and Skouby, 1993; Spona et al., 2010). A prospective cohort study compared ovarian reserve markers between users and non-users of hormonal contraception (Bentzen et al., 2012).

In a prospective study Deb et al. (2012) analysed sonographic and endocrine markers in 34 women who had been using a COC containing 30 μg EE + 150 μg levonorgestrel (LNG) with HFI for a period longer than one year, compared with 36 controls who had not used a COC within the previous year. The COC group had a significantly lower number of antral follicles measuring ≥6 mm ($P < 0.001$) and significantly lower ovarian volume, ($P < 0.001$); the vascular indices were also lower in the COC group than in controls but the number of small antral follicles measuring 2–6 mm was similar among the two groups. As regards endocrine markers, FSH, LH and oestradiol concentrations were significantly lower in the COC group ($P < 0.05$), but serum AMH concentrations were not statistically different between the two groups.

In another prospective study the authors evaluated oestradiol values and performed ultrasound scans in 87 women that used 30 μg EE + 75 μg gestodene (GSD) for two cycles. They monitored the ovarian activity by describing follicle-

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