

THE EFFECT OF MONTHLY INJECTABLE CONTRACEPTIVE MEGESTROL ACETATE COMPOUND ON PITUITARY-OVARIAN FUNCTION

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Abstract *A study of injection megestrol acetate co. on the effect of pituitary-ovarian function was carried out in 4 healthy multiparous women. The serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E_2), progesterone (P) and cortisol (F) were assayed by RIA prior to treatment and at 1st, 6th and 12th treatment cycles. The hormonal profile before injection showed normal pituitary-ovarian function with ovulation-like change. During treatment the midcycle FSH-LH surges did not occur. The basal values of FSH at the beginning of each cycle were higher than those before treatment. 24h after injection E_2 increased and persisted at high level for about 5 days and then dropped down to low level. The P levels were low throughout the whole cycle. PRL and F were in normal ranges. After treatment persistent high level of E_2 and "LH rebound action" could be seen. The above suggested that this injectable contraceptive has its effect of ovulation inhibition through suppression of midcycle peak of the gonadotrophic hormones. The follicular activity returned earlier than luteal activity. There were ovarian follicles developing in the ovaries. The rebound phenomenon of pituitary-ovarian function was present. The result of this study revealed that the effect of this injectable contraceptive on pituitary-ovarian function is mild.*

Key words *injection megestrol acetate compound pituitary-ovarian function H-P-O axis*

Résumé *L'activité de mégestrol composé injectable sur l'effet de la fonction pituitaire-ovarienne a été étudiée chez 4 femmes multipares en bonne santé. Les concentrations sériques de FSH (hormone folliculostimulante), LH (hormone lutéinisante), PRL (prolactine), E_2 (estradiol), P (progestérone) et F (cortisol) étaient titrées par RIA (essai radio-immunologique) avant le traitement et aux 1^{er}, 6^e et 12^e cycles pendant le traitement. Le profil hormonal avant l'injection avait une fonction pituitaire-ovarienne normale avec un changement*

de l'ovulation similaire. Pendant le traitement, l'augmentation de FSH-LH de l'intermédiaire du cycle ne produisait pas. Les valeurs basales de FSH au commencement de chaque cycle étaient plus hautes que celles d'avant du traitement. 24 heures après l'injection, E_2 augmentait et persistait à une haute concentration pendant 5 jours environ, et ensuite tombait à une concentration basse. Les valeurs de P étaient basses pendant tout le cycle. PRL et F étaient dans les limites normales. Après le traitement, on pouvait apercevoir une persistance d'une haute concentration de E_2 et "une action de rebondissement de LH". Les conclusions susmentionnées supposaient que le contraceptif injectable a l'effet d'une inhibition de l'ovulation par la suppression des hormones folliculaires gonadotropes au sommet de l'intermédiaire du cycle. L'activité folliculaire ovarienne développaient dans les ovaires. Le phénomène de rebondissement de la fonction pituitaire-ovarienne était présenté. Le résultat de notre étude révélait que l'effet du contraceptif injectable sur la fonction pituitaire-ovarienne est léger.

Mots clés acétate de mégestrol composé injectable fonction pituitaire-ovarienne
axe de l'H-P-O

Injection megestrol acetate compound is an effective long-acting injectable contraceptive which consists of 25mg megestrol acetate and 3.5mg 17β -estradiol. It has been widely used for more than 10 years in China. This study tries to demonstrate its chief mechanism of contraceptive action and effect on pituitary-ovarian function after injection.

MATERIALS AND METHODS

Four healthy multiparous women, aged 38-40 years, with regular menstrual cycles and without steroid medication within recent 3 months, were studied. Each subject was given two injections in the 1st menstrual cycle, one on the 5th day of the cycle and the other one week later. Thereafter only one injection was given at the 10-12th day of each cycle. Each subject received injections for 12 cycles.

Venous blood samples were taken at 8:00-10:00 a. m. every other day in the cycle prior

to treatment for self control, and every day in the 1st, 6th and 12th cycles during treatment.

In one case additional daily blood samples were collected in the cycle right after treatment. In the remaining 3 cases, daily blood samples were collected for one cycle after biphasic basal body temperature recurred.

The separated serum samples were stored at -20°C — -80°C .

All the samples were analyzed by radioimmunoassay for follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E_2) and progesterone (P). Some of them had cortisol (F) concentration assayed in the same way.

FSH and LH kits were from Amersham Co. and kits for PRL, E_2 , P and F from CIS Co.

The levels of each hormone were determined according to the direction described in the corresponding kit and all the samples of one cycle were assayed within one batch. The

coefficients of variation within and between batches were as follows:

	Coefficient of variation (%)					
	FSH	LH	PRL	E ₂	P	F
Within batches	2.8	7.2	7.7	5.54	7.75	5.59
Between batches	3.2	8.9	13.2	8.1	15	3.7

RESULTS

The hormonal profile studied before injection indicated that all subjects had normal pituitary-ovarian function with ovulation-like change.

During the period of treatment the hormonal changes of the studied cycles were as follows: The midcycle FSH-LH surges did not occur. The basal values of LH in each cycle were similar to those before treatment, whereas the basal values of FSH at the beginning of each cycle were higher than those before treatment (Fig 1). 24 hours after injection, E₂ increased and persisted at a high level for about 5 days and then dropped down to a low level on the remaining days of the cycle. In the 1st treatment cycle, blood levels of E₂ presented two peaks because of two injections (Fig 2). After that, each treatment cycle showed one E₂ peak (Fig 3). The P levels were always low throughout the whole cycle (Fig 4). PRL and F levels were in normal ranges.

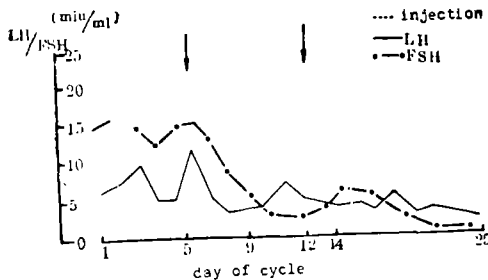


Fig 1 FSH and LH levels in the 1st treatment cycle (mean value)

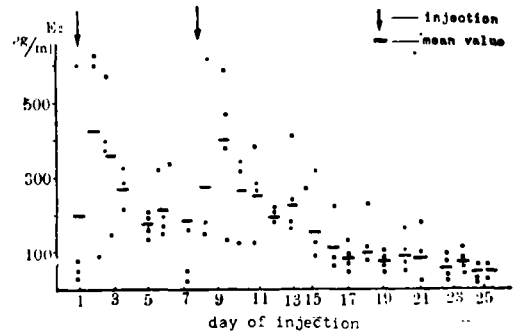


Fig 2 E₂ levels in the 1st treatment cycle

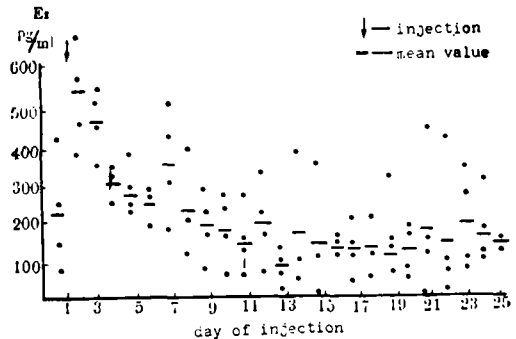


Fig 3 E₂ levels in the 6th treatment cycle

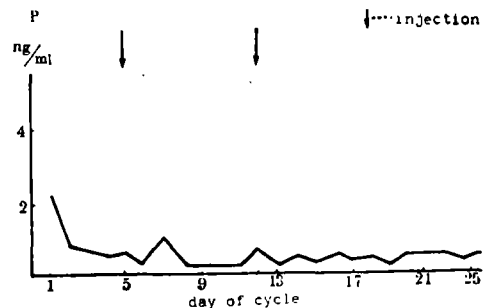


Fig 4 Progesterone levels in the 1st treatment cycle (mean value)

After treatment, the hormonal changes showed the following features: In one case in which blood samples were taken daily until the 37th day, a small LH peak appeared on the 19th day of the cycle but was lower than ovulation value. Thereafter, a small FSH peak could also be observed. Beginning on the 20th day after treatment, serum E₂ persisted at a high level for 13 days, while the serum concentration of P was still in lower state

(Fig 5). In the other 3 cases blood samples were taken daily for one cycle after biphasic basal body temperature appeared. Among these, the blood samples of one subject were taken at the 2nd cycle, the second one at the 3rd cycle and another one at the 6th cycle after treatment. The length of cycles were 20,34 and 23 days respectively. At the 7th, 20th and 9th day of each corresponding cycle the LH and FSH surges of ovulatory value were found. LH surge of the last one was much higher than the other two cases and her own pretreatment level as well (90.4 versus 62mIU/ml). Before and after LH surge E_2 peaks occurred. P levels of these 3 subjects persisted in ovulatory values (6 ng/ml) for 5-6 days after LH peaks. PRL levels had a tendency to decrease compared with those observed during the course of the treatment. Changes of serum cortisol levels were similar to those of PRL levels.

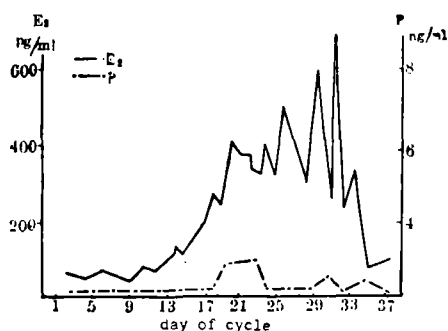


Fig 5 Case 1. E_2 and P levels right after treatment

DISCUSSION

Over more than 20 years of steroid contraceptive research it has been proven that the contraceptive efficacy is almost 100% if medication is strictly in accordance with the direction described for each contraceptive agent. The mechanism of these drugs is probably related

to their influence on reproductive processes in various ways, among which the suppression of ovulation plays the leading role. All oral and injectable contraceptives have ovulation suppression action with a characteristic phenomenon of abolishing the FSH-LH mid-cycle surge^[1-4]. The basal values of FSH and LH are similar to those observed in the early follicular phase of the menstrual cycle. LH level is lower than FSH level^[5]. It is generally believed that exogenous estrogen will decrease FSH secretion and suppress growth and maturation of follicles. So after treatment no mature ovum is found in the ovary, and of course no endogenous estrogen surge will occur before ovulation. Suppression of endogenous estrogen surge can successively cause disappearance of gonadotrophic hormone surge. Progesterone will not influence FSH secretion significantly, but will suppress LH surge in the midcycle without affecting LH basal secretion. Thus, estrogen-progesterone compound will change and decrease the secretion of FSH-LH and suppress ovulation. Therefore, steroid contraceptives will affect the development of ovarian follicles which would remain in the stage of primordial and secondary follicles^[6, 7]. After use of steroid contraceptives, in the later half of the menstrual cycle progesterone appears in low level, estrogen level remains as high as that of early follicular phase and is influenced by introduction of exogenous estrogens^[2, 8].

The results of this study are almost the same as those reported by other authors about the effect of steroid contraceptives on H-P-O axis. During treatment blood estradiol will reach the level of proliferative stage of menstrual cycle (about 100 μ g/ml), indicating that there are follicles developing in the ovaries.

This suggests that if injection is not given in time, the function of H-P-O axis may return so that contraceptive efficacy can not be guaranteed. Fotherby (1980) stated that in some women after treated with cycloprovera and low dose of progestogens, the return of follicular activity was associated with the secretion of large amount of E_2 over a long period of time, follicular activity returned earlier than luteal activity. The rise in serum E_2 levels was unlikely associated with ovulation^[9]. Such kind of hormonal changes also occurred in one subject of this study as mentioned above. In the other 3 subjects, 2—6 cycles after treatment, ovulation returned. One of them had a hyperactive luteal function (progesterone level 6ng/ml for 8 days with a peak up to 17ng/ml). Another one had a significant high value of gonadotrophin. All these data indicated quick recovery and rebound action of the H-P-O axis after treatment.

Some investigators reported that during steroid contraceptive treatment plasma cortisol is increased, and as estrogen can reduce cortisol clearance, plasma concentration of cortisol will be further increased^[10]. Our study reveals a downward tendency of serum cortisol after treatment than at the time of treatment.

In the menstrual cycle of women in child-bearing age prolactin secretion appears in irregular pattern. Generally prolactin is slightly higher at midcycle, and it is slightly lower in proliferative stage than in late luteal stage. Some reported that steroid contraceptives acting on the pituitary gland could cause decrease of gonadotrophin secretion and increase in prolactin release. There may be some relationship between amenorrhea and galactorrhea in steroid contraceptive treatment. How-

ever, personal variations are present^[11,12]. Jia Mengchun et al (1985) reported that in our country serum PRL in those treated with norgestrel compound did not reflect the same result as described above^[13]. In this study the serum PRL of all 4 cases revealed a slight upward tendency during treatment rather than after treatment. None of them had any sign of amenorrhea or galactorrhea. Although some reports considered that the side effects of steroid contraceptive bear no relation to the age of treated subject and the duration of medication^[14], different kinds of drugs and their different combinations and dosages will cause different physiological reactions^[15]. This study confirms that like other steroid contraceptives the main mechanism of this injectable contraceptive is suppression of ovulation through inhibition of pituitary-ovarian function. After varying periods of discontinuation of treatment the function of H-P-O axis returns to normal. It is well shown in this paper that this contraceptive does not affect the H-P-O axis function significantly.

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