EFFECTS OF LOW-DOSE COMBINED ORAL CONTRACEPTIVES ON FOLLICLE DEVELOPMENT

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Introduction

- Oral contraceptives are effective , a convenient family planning method worldwide, and they have revolutionized the reproductive lives of millions of women since their introduction in the 1960s.
- When combined oral contraceptives (COCs) are used correctly, the pregnancy rate is 0.1 per 100 women-years.

- The hormone content in OCs has changed dramatically over the past 30 years.
- Estrogen levels were successively lowered to **35**, to **30** and then **20 ug** to alleviate the side effects. The amount of progestin in the pills was also lowered.
- The continuous lowering of synthetic steroids in **OCs** raises the question of contraceptive efficacy.

- The purpose of this study was to evaluate the effects of different types of low-dose combined oral contraceptives on ovarian follicle development and possible implication for their efficacy and functional ovarian cyst development by diagnostic ultrasound studies.

Materials and Methods

- A MEDLINE search , using the search terms ‘Contraceptives, oral ’(MeSH) , ‘ Follicle , ovarian ’ (MeSH) , ‘Ovulation Inhibition ’ , ‘ follicular development ’ and limited to ‘ human ’ and ‘English language’, identified studies.

- A retrospective review of the literature was performed to determine the association between low-dose OCs (20 - 40 ug) and follicle development.

Results

- **1. The mechanism of inhibiting ovulation by low-dose COCs.**
- **COCs** prevent pregnancy primarily by inhibiting ovulation and by changing the cervical mucus to inhibit sperm penetration.
- The administration of **COCs** inhibits follicular development, ovulation and corpus luteum formation.

- A marked reduction of ovarian **estrogen** secretion and the shortage of **progesterone** production can be observed.
- The ovarian effects are due to the inhibitory action of **COCs** on the pituitary production and secretion of both **FSH** and **LH** , particularly on the midcycle surge of the two hormones.

- Progestational agents primarily suppress **LH** secretion, preventing the **LH** surge which is needed for ovulation. Estrogenic compounds act centrally to inhibit **FSH** secretion and inhibit follicular development. The combined administration of both compounds greatly increases the antigonadotropic and ovulation inhibition effects.

2. Ultrasonographic evaluation of ovarian activity

- **Diagnostic ultrasound is a non-invasive method for monitoring the inhibiting effect of the pill on ovarian activity.**
- **It was possible to determine the time of ovulation in more than 80 % of women by observing the changes from follicle to corpus luteum by ultrasound studies.**

3. Ultrasonographic evaluation of ovarian activity under monophasic oral contraceptives

- **The trend towards lowering the dose of contraceptive pills in order to decrease side effects could lead to increased ovarian folliculogenesis.**
- **The degree of residual ovarian activity could be a parameter of the effectiveness of oral contraceptives.**

Table 1 Low-dose regimens of monophastic combined oral contraceptives and the rate of ovarian follicle development by ultrasound studies

Auther (Year)	No.of women	Regimens	Treatment cycle	Rate of follicle development (>= 10 mm)
Karl Thomas (8) (1990)	18	30ugEE/ 75ug gestodene	3	cycle 3 : 35.2%
H.J.Hoogland (7) (1993)	89	30ugEE/ 75ug gestodene	2	US1-4days 13% 5-8days 12% 10-12days 6.8%
Ch.Egarter (9) (1995)	63	(1)35ugEE/250ug norgestimate (2)20ugEE/150ug desogestrel	2	(1) 14% (2) 14%
Ponjla Coney (3) (1999)	26	20ugEE/100ug levonorgestrel	3	62% ovulation 2.7% LUF 2.7%
John K. Jain (2) (2000)	13	20ugEE/100ug levonorgestrel	2	84.6% LUF 7.7% (>=30mm)
J.Spona (10) (1996)	24	20ugEE/100ug levonorgestrel	3	cycle 1 : 25% cycle 2 : 62.5% cycle 3 : 47.8%
J.Spona (11) (1996)	60	(1)20ugEE/75ug gestodene(21days) (2)20ugEE/75ug gestodene(23days)	3	(1) 52.2% (2) 48.9%
Winfried G (12) (1997)	118	(1)20ugEE/500ug norethisterone(n=59) (2)20ugEE/150ug desogestrel (n=59)	3	10.4% ovulation 4.1% 2.8% ovulation 2.9%
Helen Sullivan (13) (1999)	58	(1)15ugEE/60ug gestodene(21days) (2)15ugEE/75ug gestodene(24days)	3	(1) 9.3%, LUF 8% one ovulation (2) None

- Table 1 shows that the incidence of follicle development with OCs containing **30ug EE/ 75 ug gestodene** was **13 % to 35.2 %,** compared to the incidence of OCs containing **20 ug EE/ 75 gestodene 52.2 % (21 days)** and **48.9 % (23 days).**

- The rate of follicle development with treatment of preparations with **20 ug EE of monophasic COCs** were 2.8 % to 84.6 %, especially regimens with **20 ug EE/ 100 ug levonorgestrel** had a greater incidence of folliculogenesis, 25 % to 84.6 %.

Table 2 Low-dose regimens of triphastic combined oral contraceptives and the rate of ovarian follicle development by ultrasound studies

Auther (Year)	No.of women	Regimens	Treatment cycle	Rate of follicle development (>= 10 mm)
Stephen (16) (1987)	22	30ugEE/50ugLNG (6days) 40ugEE/75ugLNG (5days) 30ugEE/125ugLNG(10days) 11pers taken pill day 1 11pers taken pill day 5	1	36.4%
Stephen (17) (1989)	10	30ugEE/50ugLNG (6days) 40ugEE/75ugLNG (5days) 30ugEE/125ugLNG(10days)	3	7days pill- free 10% 10-16 days pill-free 90%
Carl J.C (18) (1989)	30	0.035mgEE/0.5mg norethindrone (7*) 0.035mgEE/0.75mg nor(7*) 0.035mgEE/1.00mg nor(7*) cycle2 : GroupI : 21days (n=12) GroupII : day 1 missed (n=9) GroupIII :day 2 missed (n=9)	2	cycle 1 : 36.7% cycle 2 : 23.3% one ovulation
Janneke (19) (1995)	31	(1) 30ugEE/50ugLNG (6*) 40ugEE/75ugLNG (5*) 30ugEE/125ugLNG(10*) (2) 35ugEE/50ugDSG (7*) 30ugEE/100ugDSG(7*) 30ugEE/150ugDSG(7*)	3	(1) 46.7 % one ovulation (2) 35.4% one LUF
Pier Giorgio (20) (1996)	60	35mgEE/50mgDSG (1-7days) 30mgEE/100mg DSG (8-10days) 30mgEE/150mg DSG (15-21days)	2	11.1%

- Table 2 shows that the incidence of follicle development with low-dose triphasic COCs was **10 % to 46.7 %** when they were treated regularly for a cycle of 21 days.

5. Low dose combined oral contraceptives and functional ovarian cysts

- **Ovarian follicular development occurs during treatment with OCs. In general, they disintegrated within about one cycle.**
- **However, there is a possibility of the development of persistent functional cysts during the use of oral contraceptives. This study showed that the incidence of luteinized unruptured follicle (LUF) with 20 ug EE / 100 ug levonorgestrel was 2.7 % - 7.7 % , compared to the incidence of 8 % with 15 ug EE / 60 ug gestodene.**

Discussion

- With the decrease in dosage there was a theoretical risk of a reduction of contraceptive safety.

- Follicle development occurs with, both **monophasic** and **triphasic** preparations. Follicle development is more often seen during the pill- free week and during the first week of OC therapy.

- more ovarian follicle development occurred with 20 ug of EE compared to OCs containing 30 ug of EE with the same types and amounts of progestins.

- The lower dose of **ethinyl estradiol** in the oral contraceptives formulation probably allows for ovarian follicular development.
- This effect is attributable to diminished **FSH** suppression.

- A greater inhibitory effect on the ovary was achieved by starting contraception on day 1 of the cycle rather than on day 5 in a triphasic OC.
- It would appear that the increase in gonadotropin production that has occurred during these 5 days makes the hypothalamo-pituitary axis less susceptible to inhibition by exogenous steroid hormones.

- **Shorter pill interval of 5 days** with a regimen containing **20 ug of EE and 75 ug of gestodene** is associated with less ovarian activity compared to a regular regimen with **a 7-day pill-free interval.**

- A clinical trial showed that follicles developing during OC cycles have the potential for **ovulation** , **but this is of doubtful clinical significance for the vast majority of women.**

- Even if ovulation were to occur , contraceptive failure would still be unlikely in view of the effect of the pill on both cervical mucus and the endometrium. Therefore, these factors may play an important role in the high contraceptive efficacy of low-dose combined oral contraceptives.

Conclusions

- (1) The same rate of contraceptive effectiveness can be maintained with **only 20 ug of estrogen** in combined oral contraceptives.
- (2) The lower dose of EE in the oral contraceptive formulation probably accounts for the greater incidence of folliculogenesis.

Conclusions

- (3) Shorter pill-free intervals decrease follicular development and might increase the contraceptive efficacy.
- (4) Ultrasound studies provide useful information for assessing the growth of follicles. Precision and reliability of ultrasound examinations is increased when done in conjunction with the measurement of hormone levels.

Acknowledgments