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Residual ovarian activity during oral steroid contraception

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Steroid drugs with contraceptive properties have been available in the clinical setting for over four decades and are still subject to improvement. Estrogens, progestins and anti-progestins have been used alone or in various combinations, regimens and routes of administration to favour the balance between efficacy and undesirable effects. One of the most important changes in this respect is the gradual lowering of steroid dosage in commercially available contraceptives. Current steroid contraceptive pills still achieve the goal of suppression of pituitary–ovarian activity, but the margins for error are minimal. In this review the available data on modes of action and the effects on suppressing pituitary–ovarian activity by different forms of oral contraception are reassessed. Although pregnancy rates provide a crude measure of contraceptive efficacy, no benchmark for pituitary–ovarian inhibition is available to test the suppressive potential of contraceptive drugs. Consequently, many studies provide incomplete and/or incomparable results. For the further study of those forms of steroid contraception that rely predominantly on suppression of ovarian activity, prevention of dominant follicles selection should be the objective.

Key words: combined oral contraception/follicle development/hypothalamic–pituitary–ovarian activity/pill-free period/progestin-only pill

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Introduction

Oral steroid contraceptives have emerged as a generally well tolerated, reversible, effective form of contraception and are extensively used worldwide. Owing to the pioneering work of Pincus *et al.* the first combined oral contraceptive (COC) containing 150 μg mestranol and 9.85 mg norethynodrel was developed in the late 1950s (Pincus *et al.*, 1958). Since the introduction of this first COC, new contraceptive techniques have provided alternative forms of steroid contraception: i.m. depot injections, subdermal implants, intrauterine delivery systems, vaginal rings and transdermal patches. Oral contraceptives (OCs) have evolved through discovery of new progestins, development of progestin-only pills and gradual lowering of the estrogen content in COCs. Biphasic and triphasic regimens appeared by changing the individual dosages for the estrogen and progestin components. All of these efforts are aimed at reducing adverse effects and improving compliance while maintaining superior efficacy over non-steroid forms of reversible contraception. However, in reducing the steroid burden to avoid adverse effects, suppression of endogenous hypothalamic–pituitary–ovarian activity could be compromised in cases of pill omissions, during the pill-free period and during co-medication (Fauser and Van Heusden, 1997). Studies addressing the influence of contraceptive steroids on the hypothalamic–pituitary–ovarian axis can be classified as shown in Table I.

The exact mode of action of contraceptive steroids in COC has not yet been satisfactorily elucidated. The majority of studies describe serum levels of FSH, LH, estradiol (E_2) or progesterone, sometimes in combination with ultrasound assessments of follicle diameters during the studied contraceptive medication. Next to these observational studies, knowledge concerning the contraceptive activity of COCs has benefited from intervention studies. GnRH, hCG or FSH intervention studies during active medication, pill omissions and the study of the pill-free period have provided critical information regarding contraceptive efficacy.

Table I. Differences in features of studies that address the influence of contraceptive steroids on the pituitary–ovarian axis

Study medication
Oral estrogen/progestagen users (mono-, bi- and triphasic schedules)
Oral progestagen-only users (mini-pill)
Systemic high-dose progestagen only users (e.g. DMPA)
Systemic estrogen/progestagen users (long-acting injectables, medicated vaginal rings)
Systemic low-dose progestagen only users (e.g. Norplant, Implanon)
Methods
Serum FSH, LH, E_2, progesterone (daily, weekly, monthly, other condition)
Ultrasound assessments of follicle diameter (daily, weekly, monthly, other condition)
Setting
Normal use (mode of action, comparative trials)
Discontinuation of use (and subsequent return to 'fertility')
Intervention (e.g. GnRH administration, hCG or FSH injections, pill omissions)
Outcome
Classification of ovarian activity
Ovulations (either based on progesterone level, ultrasound features or both)
Dominant follicles (follicle diameters >10 mm)
Descriptive data on hormones
Descriptive data on follicle growth
(Pregnancy)
Pitfalls
Different hormone assays FSH, LH, E_2 and P
Suboptimal timing/frequency study parameters
Different criteria for interpretation of the study data
Biased study population
Dissimilar effects of studied progestins
Large intra- and inter-individual variations in pharmacokinetics of used drug(s)
Large intra- and inter-individual variations hypothalamic–pituitary–ovarian response

DMPA = depot medroxyprogesterone acetate.

The focus of this review is to summarize the effects of oral steroid contraceptives on residual pituitary–ovarian activity.

Progestins

The classification of progestins is based either on chemical structure (19-nortestosteronederivatives or 17-α-acetoxyprogesteronederivatives), receptor affinity or 'relative' potency. The latter is often derived from their effects on the endometrium (Clauberg or Swyer–Greenblatt test) (Goldzieher, 1986). However, equipotency in relation to endometrial effects does not imply the same effect on other parameters such as metabolism or LH suppression. Thus the assessed 'relative potency' depends upon the target organ and the parameter studied and therefore should not be used.

Progestins are believed to exert their contraceptive effects through a variety of changes in different targets: (i) suppression of the LH surge and ovulation (Tafurt *et al.*, 1980; Barnhart *et al.*, 1997; Van Heusden *et al.*, 2000); (ii) changes in permeability of cervical mucus (Croxatto *et al.*, 1987; Kumar *et al.*, 1991); (iii) changes in endometrial receptivity for embryo implantation (Landgren *et al.*, 1990; Song and Fraser, 1995; Somkuti *et al.*, 1996); (iv) changes in tubal and uterine motility causing delayed gamete transport (Coutinho *et al.*, 1973; Paltieli *et al.*, 2000); and (v) a direct effect on the ovary (Dericks-Tan *et al.*, 1992; Kim Bjorklund *et al.*, 1992; Kuhl, 1996). The contraceptive effects of progestins on endometrium and tubal motility are speculative. However, in high doses used for post-coital contraception they appear to induce a potent contraceptive effect (Ling *et al.*, 1983; Wu *et al.*, 1999; Hapangama *et al.*, 2001).

A major target of progestins is to inhibit the LH surge in order to prevent ovulation. During the normal menstrual cycle there is a noticeable variation in the spontaneous pulsatile release of LH and response to a GnRH bolus (Yen *et al.*, 1972; Wang *et al.*, 1976). Progesterone induces low amplitude GnRH pulses and is able to block the E_2-induced LH surge at the hypothalamic level (Wildt *et al.*, 1981b; Hanker *et al.*, 1985). Administration of progestins probably induces changes in the pulsatile release of LH comparable with the late luteal phase, although this is predominantly demonstrated in women using COCs. Two studies in progestin-only users—long-term injectable depot medroxyprogesterone acetate (Perez-Lopez *et al.*, 1975) or norethindrone-enanthate (Ismail *et al.*, 1987)—failed to demonstrate differences in basal or GnRH-induced gonadotrophins compared with controls. This suggests that the pituitary is not a primary site for ovulation inhibition by these progestins. No data are available with regard to the effects of oral progestins on GnRH-stimulated pituitary response.

Although progestin-induced changes in the hypothalamic–pituitary signalling lack definite proof, changes in pituitary–ovarian activity are well documented. Studies performed by Landgren and co-workers (Landgren *et al.*, 1979, 1981; Landgren and Diczfalusy, 1980) regarding the effects of 300 µg norethisterone revealed four types of ovarian activity: (i) no activity,

although FSH levels were not suppressed (16%); (ii) follicle growth without luteal activity along with suppressed LH concentrations (23%); (iii) normal follicular development and inadequate luteinization (21%); and (iv) normal ovulatory cycles (40%). FSH and LH peak values were suppressed but mean levels remained normal. No difference in LH levels was found among women showing different types of ovarian response. In these studies, E_2 and progesterone levels comparable with an ovulatory cycle were seen despite lowered or even absent LH and FSH surge. Thus, ovarian suppression by 300 µg norethisterone alone was unrelated to the degree of inhibition of FSH and LH secretion, suggesting direct interference with ovarian function. Other studies confirm an unpredictable effect of norethisterone on ovulation suppression (Nuttall *et al.*, 1982; Song *et al.*, 1993) also when given intranasally (Shah *et al.*, 1985; Anand Kumar *et al.*, 1991). Tayob confirmed ovulation by ultrasound (Tayob *et al.*, 1985, 1986) and discovered a higher incidence of functional ovarian cysts in progestin-only pill users. In women using 75 µg desogestrel daily, however, complete suppression of ovulation was established while dominant follicles and moderate E_2 levels were commonly present (Rice *et al.*, 1996; Van Heusden *et al.*, 2000).

Data obtained from progestin implants (Norplant®, Implanon®, Uniplant®) indicate a variable degree of ovarian activity ranging from normal ovulatory cycles, luteal phase defects, luteinized unruptured follicles and complete suppression of follicle development (Shaaban *et al.*, 1984, 1993; Brache *et al.*, 1985, 2000; Alvarez *et al.*, 1986, 1996; Croxatto *et al.*, 1988; Faundes *et al.*, 1991; Shoupe *et al.*, 1991; Barnhart *et al.*, 1997; Devoto *et al.*, 1997; Makarainen *et al.*, 1998). The high degree of ovulation inhibition achieved with progestin-only implants seems to place this strategy between oral progestin-only and injectable progestin-only contraceptive methods pertaining to contraceptive efficacy.

Summarizing the effects of oral progestins on the hypothalamic–pituitary ovarian axis, it seems clear that many issues remain unsolved. The direct effect of synthetic progestins on hypothalamic GnRH secretion remains poorly understood. Pituitary function is erratic and results in a wide variety of ovarian activity including ovulation. The suppression of gonadotrophins (especially LH) appears to be dependent on both dose and type of progestin. Direct effects of progestins on the ovary are suggested but remain to be established. While some progestins can achieve high contraceptive efficacy when ovulation suppression is almost complete, undesirable bleeding patterns seem to prevent their widespread use.

Anti-progestins

Progesterone transforms the endometrium from a proliferative to a secretory state in the normal menstrual cycle. During the late follicular phase progesterone also facilitates the LH surge, which induces ovulation (Lasley *et al.*, 1975; Hoff *et al.*, 1983). Consequently, anti-progestins may also have contraceptive potential (Swahn *et al.*, 1996). Current knowledge of anti-progestins is derived from human and non-human studies (primates and rodents) in which different anti-progestins were used. Additional studies are needed to corroborate the data derived from animal studies and to identify disparity in the effects of different anti-progestins.

Mifepristone (RU 486), the prime example of a progesterone antagonist, is a 19-norsteroid with anti-progesterone and anti-glucocorticoid properties (Bygdeman *et al.*, 1993). However, in certain circumstances, anti-progestins may act as progesterone agonists or anti-estrogens. Its primary use is in post-coital contraception and termination of early pregnancy (Spitz *et al.*, 1996; Task Force on Postovulatory Methods of Fertility Regulation, 1999; Bygdeman *et al.*, 2000; Spitz *et al.*, 2000). Anti-progestins are able to establish contraceptive effects through delay of folliculogenesis, ovulation inhibition and interference with normal endometrial development. These effects depend on dosage and phase of the menstrual cycle.

During the follicular phase, administration of anti-progestins interferes with follicle growth and ovulation in a dose-dependent fashion. Single doses of anti-progestins administered before the LH peak delay the LH surge, delay folliculogenesis and lengthen the menstrual cycle (Collins and Hodgen, 1986; Baird *et al.*, 1995; Stratton *et al.*, 2000). Single or repeated administration arrests follicle development, inhibits a rise in E_2 and decreases plasma inhibin concentrations, even in low dosages (Croxatto *et al.*, 1995; Brown *et al.*, 2002). However, in case the delay is followed by ovulation, it does not affect implantation (Ghosh *et al.*, 1997). Although it is generally assumed that the principle mode of action is established through inhibition of E_2 feedback, inhibitory effects at the hypothalamus (Heikinheimo *et al.*, 1995, 1996; Kazem *et al.*, 1996), the pituitary (Van Uem *et al.*, 1989; Wolf *et al.*, 1989; Sanchez-Criado *et al.*, 1999) or a direct effect at the ovary (Dimattina *et al.*, 1986; Messinis *et al.*, 1997) have also been suggested.

Anti-progestins administered as a single high dose following the LH peak will delay development of secretory changes in the endometrium without affecting the length of the luteal phase (Kohler *et al.*, 1984; Gemzell-Danielsson *et al.*, 1994; Cameron *et al.*, 1997). This is achieved through the inhibition of progesterone-dependent down-regulation of estrogen and progesterone receptors in the endometrium (Cameron *et al.*, 1996). Late luteal administration of a single high dose does not achieve reliable contraceptive effects (Couzinet *et al.*, 1990). Very low daily doses of anti-progestins induce discrete changes in the endometrium (Danielsson *et al.*, 1997) resulting in reduced pregnancy rates (Zelinski-Wooten *et al.*, 1998; Marions *et al.*, 1999). Low-dose administration once a week does not inhibit ovulation, but delays endometrial development and impairs secretory activity (Gemzell-Danielsson *et al.*, 1996). Thus a significant decrease in pregnancy rate could be established without affecting the menstrual cycle (Marions *et al.*, 1998) even when ovulation is not consistently inhibited (Spitz *et al.*, 1993; Katkam *et al.*, 1995; Croxatto *et al.*, 1998).

Although continuous anti-progestin administration can prevent ovulation, it also affects cycle length and allows for a continuous (unopposed) influence of estrogen on the endometrium. Primate studies on the anti-progestin ZK 137 316 indicate that inhibition of progesterone action together with a blockade of estrogen-dependent proliferation can result in endometrial atrophy (Slayden *et al.*, 1998). Combining progestins and anti-progestins could allow for regular cycles while maintaining anovulation. However, simultaneous and sequential cyclic co-administration of a progestin with an anti-progestin abolishes the anti-ovulatory action of the anti-progestin or the progestin (Croxatto *et al.*, 1989;

Table II. Summary of studies on pituitary–ovarian activity during combined oral contraception. (**i**) Normal use

Reference	Medication (number of subjects)	Ultrasound assessments (follicles ⩾10 mm)[a]			Endocrine assessments
Elstein, 1974	50 mestranol + 1000 NET ($n = 5$)				No ovulation
Kuhl, 1985	30 EE + 50/75/125 LNG ($n = 11$) 30 EE + 150 DSG ($n = 11$)				3 ovulations
Doyen, 1987	Several low-dose OCs ($n = 35$)	12%			No ovulation
Killick, 1987	30/40/30 EE + 50/75/125 GSD ($n = 22$)	36%			No LH surges, no elevations of progesterone
Van der Vange, 1986	7 low dose oral contraceptives ($n = 70$)		⩾18 mm		6 suspected ovulations
		Cycle 1 29%	27%		
		Cycle 3 29%	29%		
		Cycle 6 30%	31%		
Jung-Hoffman, 1988	1 30 EE + 75 GSD ($n = 11$) 2 30 EE + 150 DSG ($n = 11$)				1 ovulation
Westcombe, 1988	30/40/30 EE + 50/75/125 LNG 1 switchers ($n = 25$) 2 first-users ($n = 21$) started on CD 5				Ovulation Switchers: 4% First-users: 24%
Hamilton, 1989	35 EE + 500/750/1000 mg NET ($n = 30$)		37%		
Thomas, 1990	30 EE + 75 GSD ($n = 25$)	Precycle: 100% Cycle 1: 33% Cycle 2: 22% Cycle 3: 44% Post-cycle: 100%			No luteal activity during OC use
Young, 1992	Sunday starters 1 20/30/35 EE + 1500 NET ($n = 16$) 2 30 EE + 1500 NET ($n = 16$) 3 placebo ($n = 16$)		>18 mm		1 pregnancy in group 2
		Cycle 1 43%			
		Cycle 2 25%			
		Cycle 3 63%			
Shaw, 1992	30/40/30 EE + 50/70/100 GSD ($n = 25$) Cycle 1, 2, 6	Cycle 1 28%			No ovulations
		Cycle 2 36%			
		Cycle 6 44%			
Grimes, 1994	Sunday starters 1 35 EE + 500/750/1000 NET ($n = 10$) 2 35 EE + 1000 NET ($n = 11$) 3 35 EE + 500 NET ($n = 11$) 4 controls ($n = 10$)		>30 mm		Ovulation 1 2% 2 0% 3 5% 4 70%
		Cycle 1 52%	10%		
		Cycle 2 29%	5%		
		Cycle 3 50%	1%		
		Cycle 4 62%	7%		
Fitzgerald, 1994	1 20 EE + 75 GSD ($n = 27$) 2 20 EE + 150 DSG ($n = 26$) 3 cycles	Cycle 1	2	3	No ovulations, 1 LUF cycle in DSG group
		1 GSD 16%	43%	27%	
		2 DSG 31%	37%	33%	
Broome, 1995	1 30/40/30 EE + 50/75/125 LNG ($n = 17$) 2 30 LNG only or 350 NET only ($n = 15$) 3 control ($n = 10$)	10–30 mm		>30 mm	
		1	24%	18%	
		2	67%	53%	
		3 70%	10%		
Van der Does, 1995	1 30/40/30EE + 50/75/125 LNG ($n = 15$) 2 35/30/30 EE + 50/100/150 DSG ($n = 16$)		>15 mm		1 LUF syndrome in group 1, 1 ovulation in group 2
		1 63%	44%		
		2 73%	60%		
Teichmann, 1995	1 30 EE + 75 GSD ($n = 153$) 2 20 EE + 150 DSG ($n = 149$)	10–30 mm	>30 mm		No ovulations observed; 1 pregnancy in group 2
		1 18%	5%		
		2 10%	2%		
Crosignani, 1996	1 35/30/30 EE + 50/100/150 DSG ($n = 22$) 2 20 EE + 150 DSG ($n = 15$) 3 20 EE + 75 GSD ($n = 14$)				No ovulations
		1 11%			
		2 13%			
		3 7%			

Table II. *Continued*

Reference	Medication (number of subjects)	Ultrasound assessments (follicles ⩾10 mm)[a]			Endocrine assessments
Spona, 1996b	20 EE + 100 LNG ($n = 24$)			>13 mm	1 woman (2 cycles) LUF
		1	17%	8%	
		2	13%	46%	
		3	9%	33%	
Rabe, 1997	1 controls ($n = 108$)	day 10–12		day 16–18	No ovulations in COC groups
	2 20/50 EE/LNG ($n = 83$)				
	3 30/40/30 EE + 50/75/125 LNG	1	44%	34%	
	4 20 EE + 150 DSG ($n = 47$)	2	6%	9%	
	($n = 53$)				
	5 30 EE + 150 DSG ($n = 59$)	3	25%	9%	
	6 30 EE + 75 GSD ($n = 16$)	4	2%	2%	
	7 35 EE + 250 NGS ($n = 33$)	5	3%	7%	
	8 35/35/35 EE + 180/215/250 NGS ($n = 38$)	6	17%	8%	
		7	13%	16%	
		8	17%	15%	
Coney, 1999	20 EE + 100 LNG ($n = 26$)				
	3% LUF				
	3% ovulation				

[a]Dominant follicles (Pache *et al.*, 1990).
All medications are abbreviated (e.g. 30 EE + 150 DSG means 30 μg ethinyl-estradiol combined with 150 μg desogestrel): EE = ethinyl-estradiol; NET = norethisterone; LNG = levonorgestrel; DSG = desogestrel; GSD = gestodene; NSG = norgestimate; LYN = lynestrenol; LUF = luteinized unruptured follicles.

Kekkonen *et al.*, 1995; Kekkonen and Lahteenmaki, 1996; Van Heusden *et al.*, 2000) but generally improves bleeding patterns.

In conclusion, the most reliable form of contraception using anti-progestins is established when given as a single high dose during the mid-cyclic phase, rendering it a rather unpractical approach. Daily doses block ovulation but may cause an unopposed estrogen effect on the endometrium, depending on the type of anti-progestin used. Low doses do not affect ovulation and delay endometrial maturation, the contraceptive effect of which lacks convincing proof.

Estrogens

It was Greenblatt who first demonstrated that conjugated equine estrogens or pellets of crystalline E_2 could inhibit ovulation (Greenblatt and Zarate, 1967; Emperaire and Greenblatt, 1969; Greenblatt *et al.*, 1974, 1977). A subsequent study established the effect of different dosages of estrogen alone or in combination with a progestin on pituitary gonadotrophin release. A progressive dose-dependent suppression of LH and FSH was observed while the addition of a progestin dramatically increased the magnitude of gonadotrophin inhibition (Goldzieher *et al.*, 1975). Later, s.c. E_2 implants (Magos *et al.*, 1987) and E_2 transdermal patches (Watson *et al.*, 1988) were also shown to be able to suppress ovulation. The exact mode of action by which estrogens induce suppression of ovulation remains to be elucidated. In castrated post-menopausal women, estrogen implants suppress gonadotrophin levels, suggesting a direct effect at the pituitary and/or hypothalamus (Thom *et al.*, 1981). Inhibitory and stimulatory effects of estrogens on gonadotrophin secretion (Yen and Tsai, 1971) along with differential effects on LH and FSH have been reported. Studies in primates suggest that the primary site of suppression of gonadotrophins is at the pituitary (Knobil, 1980). Also in primates, estrogens were able to inhibit growth of pre-antral and medium-sized antral follicles, presumably through a direct effect at the ovary (Koering *et al.*, 1991, 1994).

Combined oral contraceptives

Traditionally, the doctrine with regard to the mode of action of steroidal components in COC implicated progestins to inhibit the LH surge, whereas estrogens are required for endometrial stability and thus provide satisfactory bleeding patterns. This concept is understandable from a historical perspective, since estrogens were found fortuitously as an impurity in the first contraceptive medication. Currently a wide variety of changes attributed to both steroid components should contribute to the contraceptive effects of COCs. Decreased gonadotrophin secretion, inhibition of the LH surge, altered responsiveness to gonadotrophin stimulation, decreased cervical mucus permeability, decreased endometrial receptivity for implantation, decreased motility of the oviduct and uterus impairing gamete transport, or a direct suppressive effect on the ovary have all been proposed to explain the contraceptive efficacy of steroids. A large amount of descriptive data is available with regard to the effect of COCs on gonadotrophin and ovarian steroid levels as well as ultrasound assessments of follicular dynamics. Various investigations have been performed describing parameters of pituitary–ovarian activity during oral contraceptive regimens: alternative start of a medication-strip (Sunday starters), effect of pill omission at different moments during the pill strip, regular and extended pill-free periods and comparisons of different formulations during normal use.

Table III. Summary of studies on pituitary–ovarian activity during combined oral contraception. (**ii**) pill omissions

Reference	Medication (number of subjects)	Ultrasound assessments (follicles ⩾10 mm)[a]	Endocrine assessments
Chowdhury, 1980	30 EE + 1000 NET ($n = 54$) 2 consecutive missing pills day 7–17 1 1st cycle ($n = 35$) 2 4th cycle ($n = 19$)		Ovulations 1/10 in control group 10/35 in first cycle 7/19 in fourth cycle
Wang, 1982	30 EE + 150 LNG ($n = 32$) 1 Omission day 9 and 10 ($n = 8$) 2 11 and 12 ($n = 8$) 3 14 and 15 ($n = 8$) 4 17 and 18 ($n = 8$)		No ovulations
Smith, 1986	1 30 EE + 150 LNG ($n = 18$) 2 30/40/30 EE + 50/75/125 LNG ($n = 18$) 7, 14 or 21 days of study medication		1 ovulation following single week of triphasic medication
Letterie, 1992	35 EE + 500/750/1000 NET ($n = 15$) 1 1 missing tablet day 1–4 ($n = 5$) 2 2 missing tablets day 3–6 ($n = 5$) 3 3 missing tablets day 6–9 ($n = 5$)	No follicles >13 mm	No ovulations
Hedon, 1992	35 EE + 250 NGS ($n = 47$) Control cycles ($n = 5$) 2 cycles, 1–4 pill omissions on day 1, 6, 12, 18	19% follicles >10 mm	No ovulations
Vallon, 1992	35 EE + 250 NGS ($n = 39$) 2 study cycles, 1–4 pill omissions on day 1, 6, 12 or 18; 5 controls	Follicle >16 mm: 6/39	No ovulations

[a]Dominant follicles (Pache *et al.*, 1990).
All medications are abbreviated (e.g. 30 EE + 150 DSG means 30 µg ethinyl-estradiol combined with 150 µg desogestrel): EE = ethinyl-estradiol; NET = norethisterone; LNG = levonorgestrel; DSG = desogestrel; GSD = gestodene; NSG = norgestimate; LYN = lynestrenol.

Normal use

The general conclusion from studies performed to investigate pituitary–ovarian activity during COC use (for overview of individual studies see Table II) is a gradual decline of gonadotrophins in the first week of medication leading to the suppression of development of non-dominant follicles and subsequent E_2 demise. In case dominant follicles are present at the start of COC, they can still increase in diameter and even reach cystic proportions (>30 mm). Delayed start of a new COC cycle (i.e. 'Sunday starters') increases the risk of dominant follicles emerging and should therefore be discouraged (Killick *et al.*, 1987; Danforth and Hodgen, 1989). Despite increase in follicular diameter during active medication, E_2 levels eventually decrease, probably as a result of very low LH levels due to the two gonadotrophin 2-cell hypothesis (Schoot *et al.*, 1992). Although this raises questions with regard to 'the functional life span' of these follicles (Kettel *et al.*, 1991; Shaw *et al.*, 1992; Faundes *et al.*, 1996), it appears that the potential to ovulate remains (Killick, 1989).

Virtually all commercially available COCs combine ethinyl-estradiol (some of the older preparations in the US still contain mestranol) with a synthetic progestin. A new combination containing 1 mg micronized 17-β-estradiol (1 mg E_2 + 150 µg desogestrel) has been shown to inhibit ovulation (Schubert and Cullberg, 1987; Wenzl *et al.*, 1993; Csemiczky *et al.*, 1996). The additional contraceptive effect of E_2 remains to be established since 75 µg desogestrel alone also appears to be able to inhibit ovulation effectively (Van Heusden *et al.*, 2000). The extent of pituitary–ovarian suppression appears to be related to the dose of ethinyl-estradiol in COCs while the type of progestin is less important (Spellacy *et al.*, 1980; Mall Haefeli *et al.*, 1991; Fauser and Van Heusden, 1997; Van Heusden and Fauser, 1999).

Pill omissions

The effect of pill omissions during COC use is related to the moment in the pill cycle and the number of pills missed (for summaries of relevant studies see Table III). Suppression of pituitary–ovarian activity increases with the number of pills already taken and maximum suppression is often encountered at the end of the COC cycle (Smith *et al.*, 1986). High-dosed COCs may reach maximum suppression after only 7 days (Van Heusden *et al.*, 2002). Once maximum suppression is achieved, up to seven pills can be omitted (i.e. the pill-free period). Extending these 7 days easily leads to the development of dominant follicles that continue to grow, even when OC therapy is recommenced (see also Figure 1). The administration of hCG was able to induce ovulation and luteinization in these women (Killick, 1989). However, the initial LH peak after stopping COC occurred 21–28 days thereafter (Klein and Mishell, 1977). This effect may be ethinyl-estradiol dose-related (Bracken *et al.*, 1990).

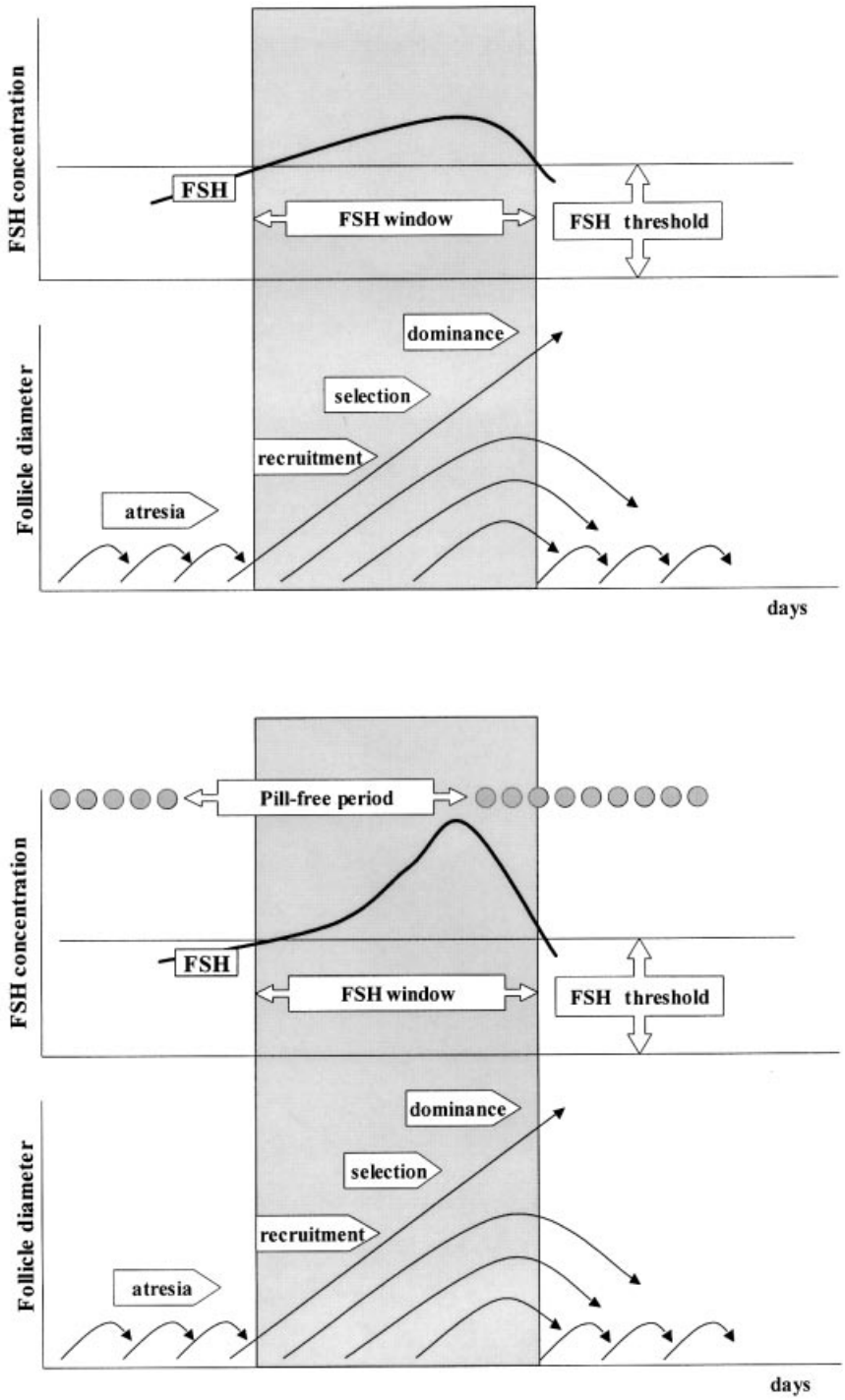

Figure 1. Schematic representation of changes over time in serum FSH concentrations and ovarian follicles comparing the luteo-follicular transition in normo-ovulatory women (upper panel) and the pill-free period in COC users (bottom panel). For further detailed description and background information with regard to follicle recruitment, selection and dominance see Fauser and Van Heusden, 1997.

Determination of the moment of maximum suppression of pituitary–ovarian activity during any COC regimen is therefore mandatory to allow safe instructions for women who omit pills (Molloy *et al.*, 1985; Guillebaud, 1987). The high prevalence of pill omissions (up to 27% in 3 months) (Finlay and Scott, 1986; Klitsch, 1991) and the subsequent risk of contraceptive failure (Fraser and Jansen, 1983; Grady *et al.*, 1986; Trussell and Kost, 1987) indicate the necessity of increasing contraceptive safety to cope with the problem of pill omissions.

The pill-free period

The standard regimen of COCs allows for a pill-free (or at least steroid-free) interval of generally 7 days for eliciting regular withdrawal bleedings. During this period, pituitary–ovarian

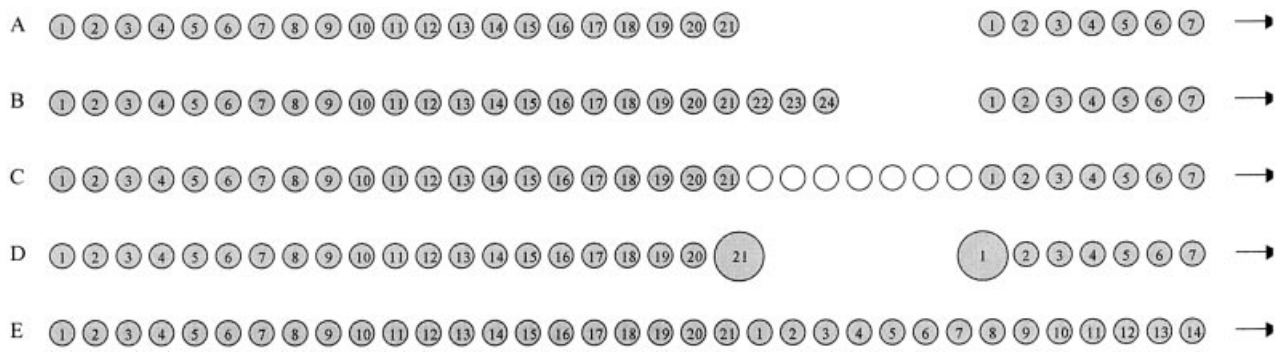

Figure 2. Strategies for reducing residual pituitary–ovarian activity during the pill-free period in combined oral contraceptives. (**A**) Traditional pill-free period of 7 days between two medication cycles of 21 days. (**B**) Shorten the pill-free period, e.g. 24 active pills and four placebo. (**C**) Use progestin-only or estrogen-only medication during former pill-free period. (**D**) Start and finish 21 medication cycle with high-dose 'sentinel' pill. (**E**) Continuous OC use until bleeding occurs and allow pill-free period of 7 days.

Table IV. Summary of studies on pituitary–ovarian activity during combined oral contraception. (**iii**) Normal pill-free interval

Reference	Medication (number of subjects) (follicles ⩾10 mm)[a]	Ultrasound assessments		Endocrine assessments
Tayob, 1990	Several low-dose COCs ($n = 120$)		23%	
Elomaa, 1998	1 30 EE + 75 GSD ($n = 34$)		>12 mm	No ovulations
	2 30/40/30 EE + 50/70/100 GSD ($n = 34$)	1	9%	
	3 20 EE + 150 DSG ($n = 31$)	2	6%	
	3 27%			
van Heusden, 1999	1 20 EE + 75 GSD ($n = 15$) 1 27%			No ovulations
	2 20 EE + 150 DSG ($n = 17$)	2	18%	
	3 30 EE + 150 DSG ($n = 12$)	3	0%	
Sullivan, 1999	15 EE + 60 GSD			1 ovulation and 6 LUF in 7 day PFP group
	1 7 day PFP ($n = 24$)	1	64%	
	2 4 day PFP ($n = 27$)	2	75%	

[a]Dominant follicles (Pache *et al.*, 1990).
All medications are abbreviated (e.g. 30 EE + 150 DSG means 30 µg ethinyl-estradiol combined with 150 µg desogestrel): EE = ethinyl-estradiol; NET = norethisterone; LNG = levonorgestrel; DSG = desogestrel; GSD = gestodene; NSG = norgestimate; LYN = lynestrenol; LUF = luteinized unruptured follicles.

activity recovers following the waning inhibitory effects of contraceptive steroids. Consequently, gonadotrophin-dependent follicle growth is initiated until the beginning of the next medication strip, after which inhibition of the pituitary–ovarian axis is re-established. Events during the pill-free period resemble those observed during the early follicular phase of the normal menstrual cycle (Figure 1). FSH levels increase above the threshold for ovarian stimulation allowing gonadotrophin-dependent follicle growth and subsequent estrogen production (Fauser and Van Heusden, 1997; Macklon and Fauser, 2000). Single dominant follicle development in the normal menstrual cycle coincides with a decrease in serum FSH concentrations (Pache *et al.*, 1990; van Santbrink *et al.*, 1995).

Resumption of contraceptive medication at the end of the pill-free period decreases FSH levels irrespective of whether dominant follicles are present or not. If no dominant follicles are present, complete suppression of folliculogenesis ensues providing optimal contraceptive safety. Should dominant follicle selection have occurred during the pill-free period, follicle growth is likely to continue during OC treatment (Van Heusden and Fauser, 1999; Van Heusden *et al.*, 2002). Under these circumstances contraceptive efficacy depends on prevention of ovulation achieved through LH-surge inhibition. The decrease in the estrogen content of low-dose COCs therefore increases the risk of the development of dominant follicles during the pill-free period. Either reduced pituitary–ovarian suppression at the beginning of the pill-free period or less suppression at the beginning of a new OC cycle allows for an increased duration of the FSH window resulting in dominant follicle development (see Figure 1). Consequently, a further reduction of the estrogen dose in COCs should be accompanied a change in the paradigm of a 7 day steroid-free interval (Van Heusden and Fauser, 1996). Shortening of the pill-free period by increasing the number of contraceptive pills per cycle (Spona *et al.*, 1996a) or adding estrogen-only pills (Killick *et al.*, 1998) more effectively suppresses the recovery of pituitary–ovarian activity and may therefore increase the contraceptive efficacy of sub-30 COCs. Some strategies to reduce the pituitary–ovarian activity during the pill-free period are summarized in Figure 2. A summary of studies on pituitary–ovarian activity in normal pill-free periods is given in Table IV, and in extended pill-free periods in Table V.

Table V. Summary of studies on pituitary–ovarian activity during combined oral contraception. (**iv**) Extended pill-free interval

Reference	Medication (number of subjects)	Ultrasound assessments (follicles ⩾10 mm)[a]	Endocrine assessments
Landgren, 1984	30 EE + 150 LNG ($n = 10$) No ovulations Extending pill free interval to 9 days in 2 consecutive cycles		
Hamilton, 1989	35 EE + 500/750/1000 NET ($n =$ 1 pill omission day 1 or 2 cycle 2 30)	7/30 >14 mm during cycle 2	2 cases of luteinization of which 1 likely to be ovulation
Killick, 1989	30/40/30 EE + 50/75/125 LNG ($n = 10$) extending pill-free interval until follicle (12 mm) appeared	Median time to follicle 12 mm after last pill : 11 days (7–16) 2/10 no follicles >18 mm 8/10 ovulation occurred after 5000 IU hCG and follicle >18 mm	
Kilick, 1990	1 30 EE + 150 LNG ($n = 10$) 2 30/40/30 + 50/75/125 LNG ($n = 9$) 3 30 EE + 75 GSD ($n = 9$) extended PFP to 9 or 11 days	>18 mm 11%	No ovulations
Landgren, 1991	1 30 EE + 150 DSG ($n = 10$) 1 ovulation in each group 2 30/40/30 EE + 50 /75/125 LNG ($n = 10$) extended PFP to 10 days		
Elomaa, 1998	1 30 EE + 75 GSD ($n = 34$) 2 30/40/30 EE + 50/70/100 GSD ($n = 34$) 3 20 EE + 150 DSG ($n = 31$) PFP extended to 10 days	>12 mm / >18 mm 1 41% / 24% 2 47% / 24% 3 70% / 40%	No ovulations 1 LUF in group 1

[a]Dominant follicles (Pache *et al.*, 1990).
All medications are abbreviated (e.g. 30 EE + 150 DSG means 30 µg ethinyl-estradiol combined with 150 µg desogestrel): EE = ethinyl-estradiol; NET = norethisterone; LNG = levonorgestrel; DSG = desogestrel; GSD = gestodene; NSG = norgestimate; LYN = lynestrenol; PFP = pill-free period.

Interventions during COC

Especially in COC users, baseline gonadotrophin levels as well as concentrations following the administration of GnRH are used to assess the magnitude of negative steroid feedback at the hypothalamic–pituitary level. However, the interpretation of these findings is not without difficulties due to the assumption that a diminished gonadotrophin response following GnRH administration should solely represent suppression by the contraceptive steroids. However, the response of the pituitary to a bolus dose of GnRH is also dependent on previous endogenous GnRH stimulation (also referred to as a 'priming effect') (Wildt *et al.*, 1981a).

The prevention of ovulation in COC is thought to occur primarily by interfering with GnRH release (Schally *et al.*, 1970). Proof of this contention is brought about by the notion that the contraceptive effect of COC can be reversed by administering GnRH. Although GnRH administration should result in an increase of LH and FSH, levels are lower suggesting an inhibitory effect of COCs at both the hypothalamus and the pituitary level. A direct effect on the pituitary is also suggested since repeated GnRH administration does not always result in an LH and FSH response (De Leo *et al.*, 1991).

Pituitary suppression appears to be unrelated to the age of the women and duration of COC use (Scott *et al.*, 1978a), but is dependent on the amount and type of progestin (Rommler *et al.*, 1982; Hemrika *et al.*, 1993) and the amount of ethinyl-estradiol (Scott *et al.*, 1978b). Furthermore, suppression of basal and GnRH-stimulated gonadotrophin release is time-dependent, i.e. lower doses need more time to establish suppression (Kuhl *et al.*, 1982, 1984; Rommler *et al.*, 1985). The suppressive effect on basal and stimulated gonadotrophin release is also present in the first days of the pill-free period (Rubinstein *et al.*, 1978). Administration of several doses of recombinant FSH during high-dose COC use resulted in dose-dependent follicle growth despite extremely low LH levels (Van Heusden *et al.*, 2002). Dominant follicles remained present following discontinuation of FSH and ongoing OC treatment suggesting that a direct effect, if any, of contraceptive steroids on dominant follicle growth is negligible. Once preovulatory follicles are present during COC use, the administration of either a GnRH analogue (Elomaa and Lahteenmaki, 1999) or hCG (Killick, 1989) can induce ovulation.

Interpretation of pituitary–ovarian activity during steroid contraception

Many studies concerning pituitary–ovarian activity during steroid contraception are seriously devalued in their relevance due to study design and/or interpretation of results. Infrequent (once per cycle) or conditional monitoring ('when a follicle of >12 mm appears') in most studies allows for major under-reporting of relevant events related to residual ovarian activity during steroid contraception. Despite early knowledge concerning the moment of ovulation in COC cycles, many studies focus on the second part of the cycle to assess ovulation. Obviously, the use of different assessments (urinary estrogens versus serum E_2), hormone assays, sampling intervals and transvaginal or transabdominal ultrasound

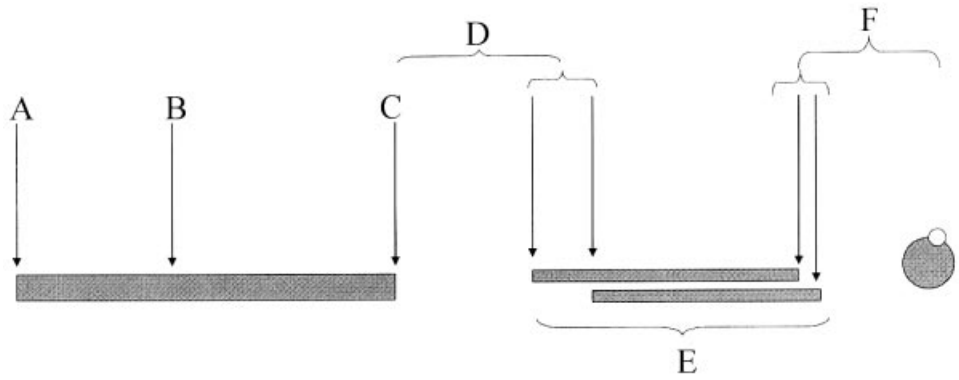

Figure 3. Proposal for uniform design in testing contraceptive effects on the pituitary–ovarian axis. (**A**) Start of regular COC cycle: magnitude of pituitary–ovarian activity to control with studied COC. (**B**) Number of pill days to achieve maximum suppression (compare with **C**). (**C**) End of regular cycle; expected maximum suppression of pituitary activity. (**D**) Number of days for individual subjects to reach a follicle >11 mm. (**E**) COC is started when follicle ⩾11 mm; number of pill days until a follicle of ⩾18 mm is observed. (**F**) COC is discontinued when a follicle of ⩾18 mm is observed; number of days until ovulation occurs.

(Belaisch-Allart *et al.*, 1991) further reduce the possibility of comparing results. Moreover, large intra- and inter-individual differences are present in contraceptive steroid serum levels, pharmacokinetics and pharmacodynamics (Jung-Hoffmann and Kuhl, 1990; Shaw *et al.*, 1992; Fitzgerald *et al.*, 1994). The origin of these differences and their consequences remain largely unexplained.

In several studies the occurrence of ovulation as a parameter of contraceptive efficacy is based upon serum progesterone levels. Different cut-off levels are used: >3 ng/ml (Kuhl *et al.*, 1985; Westcombe *et al.*, 1988), >4 ng/ml (Chowdhury *et al.*, 1980), >5 ng/ml (Rabe *et al.*, 1997) or >16 nmol/l (Song *et al.*, 1993) and >25 nmol/l (Fitzgerald *et al.*, 1994). However, the assessment of ovulation based on progesterone levels may be of limited significance in evaluating the contraceptive properties of COCs. A rise in progesterone concentration in serum merely indicates luteal activity and hence is unable to discriminate between ovulation, premature luteinization or luteinized unruptured follicles. It is also speculative whether progesterone levels will always rise following ovulation during COC use. Progesterone production requires both FSH and LH, which may be suppressed to such an extent that normal steroid biosynthesis by the corpus luteum is compromised.

Classifications combining ultrasound assessments of follicle development (diameter, signs of ovulation) and hormonal parameters have been proposed (Landgren and Diczfalusy, 1980; Hoogland and Skouby, 1993; Van Heusden and Fauser, 1996) and used or modified by others (Fitzgerald *et al.*, 1994; Van der Does *et al.*, 1995; Spona *et al.*, 1996b). This method simplifies comparison between medications, studied cycles and individuals. A classification involves establishment of maximum ovarian activity during a studied cycle. However, relevant information is lost with regard to the timing of this event during the COC cycle. Furthermore, some findings (e.g. when ultrasound assessments and endocrine assessment differ) remain unclassifiable (Barbosa *et al.*, 1990). Currently, there is no commonly accepted classification.

Benchmarking for different forms of steroid contraception requires the assessment of a combination of ultrasound and hormonal parameters, frequent sampling and a study design that allows for comparison and clinical application. We propose a design involving objective verifiable criteria for future use in studies with regard to pituitary–ovarian activity and COC use which allows for maximum clinical usefulness (Figure 3).

Conclusions

The concomitant administration of estrogens and progestins renders it difficult to evaluate the individual contribution of each entity with regard to suppression of the hypothalamic–pituitary–ovarian axis. However, effects of combined oral contraceptives have proven to be more than the sum of effects induced by either estrogens or progestins alone.

Many studies have been performed, but comparison is often hampered by suboptimal design or incomplete results. No study design has yet evolved as a benchmark for contraceptive reliability. Although inhibition of follicle growth and ovulation is well understood, little is known with regard to the effects of contraceptive steroids on other systems controlling gonadotrophin secretion.

References

Alvarez, F., Brache, V., Tejada, A.S. and Faundes, A. (1986) Abnormal endocrine profile among women with confirmed or presumed ovulation during long-term NORPLANT® use. *Contraception*, **33**, 111–119.

Alvarez, F., Brache, V., Faundes, A., Tejada, A.S. and Thevenin, F. (1996) Ultrasonographic and endocrine evaluation of ovarian function among Norplant® implants users with regular menses. *Contraception*, **54**, 275–279.

Anand Kumar, T.C., Shah, R.S., Chitlange, S.M., Hazari, K.T., Gopalkrishnan, K., Vadigoppula, A.D., Vernekar, V.J., Borkar, D.M. and Puri, C.P. (1991) Effects of intranasal administration of norethisterone on folliculogenesis, cervical mucus, vaginal cytology, endometrial morphology and reproductive-endocrine profile in women. *Contraception*, **44**, 245–267.

Baird, D.T., Thong, K.J., Hall, C. and Cameron, S.T. (1995) Failure of oestrogen induced luteinizing hormone surge in women treated with mifepristone (RU 486) every day for 30 days. *Hum. Reprod.*, **10**, 2270–2276.

Barbosa, I., Bakos, O., Olsson, S., Odlind, V. and Johansson, E.D.B. (1990) Ovarian function during use of a levonorgestrel-releasing IUD. *Contraception*, **42**, 51–66.

Barnhart, K., Devoto, L., Pommer, R., Sir-Pettermann, T., Robinovic, J. and Coutinho, E. (1997) Neuroendocrine mechanism of anovulation in users of contraceptive subdermal implant of nomegestrol acetate (Uniplant). *Fertil. Steril.*, **67**, 250–255.

Belaisch-Allart, J., Dufetre, C., Allart, J.P. and de Mouzon, J. (1991)

Comparison of transvaginal and transabdominal ultrasound for monitoring follicular development in an in-vitro fertilization programme. *Hum. Reprod.*, **6**, 688–689.

Brache, V., Faundes, A., Johansson, E. and Alvarez, F. (1985) Anovulation, inadequate luteal phase and poor sperm penetration in cervical mucus during prolonged use of Norplant® implants. *Contraception*, **31**, 261–273.

Brache, V., Massai, R., Mishell, D.R., Moo-Young, A.J., Alvarez, F., Salvatierra, A.M., Cochon, L., Croxatto, H., Robbins, A. and Faundes, A. (2000) Ovarian function during use of Nestorone® subdermal implants. *Contraception*, **61**, 199–204.

Bracken, M.B., Hellenbrand, K.G. and Holford, T.R. (1990) Conception delay after oral contraceptive use: the effect of estrogen dose. *Fertil. Steril.*, **53**, 21–27.

Broome, M., Clayton, J. and Fotherby, K. (1995) Enlarged follicles in women using oral contraceptives. *Contraception*, **52**, 13–16.

Brown, A., Cheng, L., Lin, S. and Baird, D.T. (2002) Daily low-dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days. *J. Clin. Endocrinol. Metab.*, **87**, 63–70.

Bygdeman, M., Swahn, M.L., Gemzell-Danielsson, K. and Svalander, P. (1993) Mode of action of RU 486. *Ann. Med.*, **25**, 61–64.

Bygdeman, M., Gemzell, D.K., Marions, L. and Swahn, M. (2000) Pregnancy termination. *Steroids*, **65**, 801–805.

Cameron, S.T., Critchley, H.D., Buckley, C.H., Chard, T., Kelly, R.W. and Baird, D.T. (1996) The effects of post-ovulatory administration of onapristone on the development of a secretory endometrium. *Hum. Reprod.*, **11**, 40–49.

Cameron, S.T., Critchley, H.O., Buckley, C.H., Kelly, R.W. and Baird, D.T. (1997) Effect of two antiprogestins (mifepristone and onapristone) on endometrial factors of potential importance for implantation. *Fertil. Steril.*, **67**, 1046–1053.

Chowdhury, V., Joshi, U.M., Gopalkrishna, K., Betrabel, S., Mehta, S. and Saxena, B.N. (1980) 'Escape' ovulation in women due to the missing of low dose combination oral contraceptive pills. *Contraception*, **22**, 241–247.

Collins, R.L. and Hodgen, G.D. (1986) Blockade of the spontaneous midcycle gonadotropin surge in monkeys by RU 486: A progesterone antagonist or agonist? *J. Clin. Endocrinol. Metab.*, **63**, 1270–1276.

Coney, P. and DelConte, A. (1999) The effects on ovarian activity of a monophasic oral contraceptive with 100 microg levonorgestrel and 20 microg ethinyl estradiol. *Am. J. Obstet. Gynecol.*, **181**, 53–58.

Coutinho, E.M., Maia, H. and da Costa, R.X. (1973) The effect of a continuous low dose progestin on tubal and uterine motility. *Int. J. Fertil.*, **18**, 161–166.

Couzinet, B., Le Strat, N., Silvestre, L. and Schaison, G. (1990) Late luteal administration of the antiprogesterone RU486 in normal women: effects on the menstrual cycle events and fertility control in a long-term study. *Fertil. Steril.*, **54**, 1039–1044.

Crosignani, P.G., Testa, G., Vegetti, W. and Parazzini, F. (1996) Ovarian activity during regular oral contraceptive use. *Contraception*, **54**, 271–273.

Croxatto, H.B., Diaz, S., Salvatierra, A.M., Morales, P., Ebensperger, C. and Brandeis, A. (1987) Treatment with Norplant subdermal implants inhibits sperm penetration through cervical mucus *in vitro*. *Contraception*, **36**, 193–201.

Croxatto, H.B., Diaz, S., Pavez, M. and Brandeis, A. (1988) Estradiol plasma levels during long-term treatment with Norplant(R) subdermal implants. *Contraception*, **38**, 465–475.

Croxatto, H.B., Salvatierra, A.M., Fuentealba, B. and Massai, R. (1989) Contraceptive potential of a mifepristone-nomegestrol acetate sequential regimen in women. *Hum. Reprod.*, **13**, 3297–3302.

Croxatto, H.B., Salvatierra, A.M., Fuentealba, B. and Leiva, L. (1995) Follicle stimulating hormone-granulosa cell axis involvement in the antifolliculotrophic effect of low dose mifepristone (RU486). *Hum. Reprod.*, **10**, 1987–1991.

Croxatto, H.B., Kovacs, L., Massai, R., Resch, B.A., Fuentealba, B., Salvatierra, A.M., Croxatto, H.D., Zalanyi, S., Viski, S. and Krenacs, L. (1998) Effects of long-term low-dose mifepristone on reproductive function in women. *Hum. Reprod.*, **13**, 793–798.

Csemiczky, G., Dieben, T., Coelingh Bennink, H.J.T. and Landgren, B.M. (1996) The pharmacodynamic effects of an oral contraceptive containing 3 mg micronized 17 beta-estradiol and 0.150 mg desogestrel for 21 days, followed by 0.030 mg desogestrel only for 7 days. *Contraception*, **54**, 333–338.

Danforth, D.R. and Hodgen, G.D. (1989) 'Sunday start' multiphasic oral contraception: Ovulation prevention and delayed follicular atresia in primates. *Contraception*, **39**, 321–330.

Danielsson, K.G., Swahn, M.L., Westlund, P., Johannisson, E., Seppala, M. and Bygdeman, M. (1997) Effect of low daily doses of mifepristone on ovarian function and endometrial development. *Hum. Reprod.*, **12**, 124–131.

De Leo, V., Lanzetta, D., Vanni, A.L., D'Antona, D. and Severi, F.M. (1991) Low estrogen oral contraceptives and the hypothalamo-pituitary axis. *Contraception*, **44**, 155–161.

Dericks-Tan, J.S.E., Gudacker, V. and Taubert, H.D. (1992) Influence of oral contraceptives on integrated secretion of gonadotropins. *Contraception*, **46**, 369–377.

Devoto, L., Kohen, P., Barnhart, K., Alba, F., Pommer, R., Retamales, I. and Coutinho, E. (1997) Hormonal profile, endometrial histology and ovarian ultrasound assessment during 1 year of nomegestrol acetate implant (Uniplant registered). *Hum. Reprod.*, **12**, 708–713.

Dimattina, M., Albertson, B., Seyler, D.E., Loriaux, D.L. and Falk, R.J. (1986) Effect of the antiprogestin RU486 on progesterone production by cultured human granulosa cells: Inhibition of the ovarian 3B-hydroxysteroid dehydrogenase. *Contraception*, **34**, 199–206.

Doyen, J., Schaaps, J.P. and Lambotte, R. (1987) Ultrasonic and hormonal monitoring of the ovaries during mini-dose oral contraception. *Contracept. Fertil. Sex.*, **15**, 529–533.

Elomaa, K. and Lahteenmaki, P. (1999) Ovulatory potential of preovulatory sized follicles during oral contraceptive treatment. *Contraception*, **60**, 275–279.

Elomaa, K., Rolland, R., Brosens, I., Moorrees, M., Deprest, J., Tuominen, J. and Lahteenmaki, P. (1998) Omitting the first oral contraceptive pills of the cycle does not automatically lead to ovulation. *Am. J. Obstet. Gynecol.*, **179**, 41–46.

Elstein, M., Briston, P.G., Jenkins, M., Kirk, D. and Miller, H. (1974) Effects of a low-oestrogen oral contraceptive on urinary excretion of luteinizing hormone and ovarian steroids. *Br. Med. J.*, 11–13.

Emperaire, J.C. and Greenblatt, R.B. (1969) Contraception by implantation of estradiol pellets. *Gynecol. Prat.*, **20**, 327–335.

Faundes, A., Alvarez Sanchez, F., Brache, V., Jimenez, E. and Tejada, A.S. (1991) Hormonal changes associated with bleeding during low dose progestogen contraception delivered by Norplant subdermal implants. *Adv. Contracept.*, **7**, 85–94.

Faundes, A., Brache, V. and Alvarez, F. (1996) Functional life-span of the dominant follicle in pharmacologically induced anovulatory cycles. *Hum. Reprod.*, **11**, 114–116.

Fauser, B.C.J.M. and Van Heusden, A.M. (1997) Manipulation of human ovarian function: physiological concepts and clinical consequences. *Endocr. Rev.*, **18**, 71–106.

Finlay, I.G. and Scott, M.G. (1986) Patterns of contraceptive pill taking in an inner city practice. *Br. Med. J. (Clin. Res. Ed.)*, **293**, 601–602.

Fitzgerald, C., Feichtinger, W., Spona, J., Elstein, M., Ludicke, F., Muller, U. and Williams, C. (1994) A comparison of the effects of two monophasic low dose oral contraceptives on the inhibition of ovulation. *Adv. Contracept.*, **10**, 5–18.

Fraser, I.S. and Jansen, R.P. (1983) Why do inadvertent pregnancies occur in oral contraceptive users? Effectiveness of oral contraceptive regimens and interfering factors. *Contraception*, **27**, 531–551.

Gemzell-Danielsson, K., Svalander, P., Swahn, M.L., Johannisson, E. and Bygdeman, M. (1994) Effects of a single post-ovulatory dose of RU486 on endometrial maturation in the implantation phase. *Hum. Reprod.*, **9**, 2398–2404.

Gemzell-Danielsson, K., Westlund, P., Johannisson, E., Swahn, M.L., Bygdeman, M. and Seppala, M. (1996) Effect of low weekly doses of mifepristone on ovarian function and endometrial development. *Hum. Reprod.*, **11**, 256–264.

Ghosh, D., Nayak, N.R. and Sengupta, J. (1997) Effect of follicular phase administration of mifepristone (RU486) on blastocyst implantation in the rhesus monkey. *Contraception*, **56**, 117–122.

Goldzieher, J.W. (1986) Use and misuse of the term potency with respect to oral contraceptives. *J. Reprod. Med.*, **31**, 533–539.

Goldzieher, J.W., de la Pena, A., Chenault, C.B. and Cervantes, A. (1975) Comparative studies of etynyl estrogens used in oral contraceptives. III. Effect on plasma gonadotropins. *Am. J. Obstet. Gynecol.*, **122**, 625–636.

Grady, W.R., Hayward, M.D. and Yagi, J. (1986) Contraceptive failure in the United States: estimates from the 1982 National Survey of Family Growth. *Fam. Plann. Perspect.*, **18**, 200–209.

Greenblatt, R.B. and Zarate, A. (1967) Effect of quinestrol on ovulation. *Int. J. Fertil.*, **12**, 243–246.

Greenblatt, R.B., Hernandez-Ayup, S. and Bohler, C.S. (1974) Estradiol pellet implantation for contraception. *J. Reprod. Med.*, **13**, 207–208.

Greenblatt, R.B., Asch, R.H., Mahesh, V.B. and Bryner, J.R. (1977) Implantation of pure crystalline pellets of estradiol for conception control. *Am. J. Obstet. Gynecol.*, **127**, 520–524.

Grimes, D.A., Godwin, A.J., Rubin, A., Smith, J.A. and Lacarra, M. (1994) Ovulation and follicular development associated with three low-dose oral contraceptives: a randomized controlled trial. *Obstet. Gynecol.*, **83**, 29–34.

Guillebaud, J. (1987) The forgotten pill—and the paramount importance of the pill-free week. *Br. J. Fam. Plann.*, **12**, 35–43.

Hamilton, C.J.C.M. and Hoogland, H.J. (1989) Longitudinal ultrasonographic study of the ovarian suppressive activity of a low-dose triphasic oral contraceptive during correct and incorrect pill intake. *Am. J. Obstet. Gynecol.*, **161**, 1159–1162.

Hanker, J.P., Nieschlag, E. and Schneider, H.P. (1985) Hypothalamic site of progesterone action on gonadotropin release. *Horm. Metab. Res.*, **17**, 679–682.

Hapangama, D., Glasier, A.F. and Baird, D.T. (2001) The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception*, **63**, 123–129.

Hedon, B., Cristol, P., Plauchut, A., Vallon, A.M., Desachampts, F., Taillant, M.L., Mares, P., Pizelle, A.M., Laffargue, F. and Viala, J.L. (1992) Ovarian consequences of the transient interruption of combined oral contraceptives. *Int. J. Fertil.*, **37**, 270–276.

Heikinheimo, O., Gordon, K., Lahteenmaki, P., Williams, R.F. and Hodgen, G.D. (1995) Antiovulatory actions of RU 486: the pituitary is not the primary site of action *in vivo*. *J. Clin. Endocrinol. Metab.*, **80**, 1859–1868.

Heikinheimo, O., Gordon, K., Williams, R.F. and Hodgen, G.D. (1996) Inhibition of ovulation by progestin analogs (agonists vs antagonists): preliminary evidence for different sites and mechanisms of actions. *Contraception*, **53**, 55–64.

Hemrika, D.J., Slaats, E.H., Kennedy, J.C., De Vries Robles Korsen, T.J.M. and Schoemaker, J. (1993) The effects of levonorgestrel, desogestrel and gestodene on the pulsatile release of luteinizing hormone in oral contraceptive users. *Gynecol. Endocrinol.*, **7**, 191–200.

Hoff, J.D., Quigley, M.E. and Yen, S.S. (1983) Hormonal dynamics at midcycle: a reevaluation. *J. Clin. Endocrinol. Metab.*, **57**, 792–796.

Hoogland, H.J. and Skouby, S.O. (1993) Ultrasound evaluation of ovarian activity under oral contraceptives. *Contraception*, **47**, 583–590.

Ismail, A.A., El Faras, A., Rocca, M. and el Sibai, F.A. (1987) Pituitary response to LHRH in long-term users of injectable contraceptives. *Contraception*, **35**, 487–495.

Jung-Hoffmann, C. and Kuhl, H. (1990) Intra- and interindividual variations in contraceptive steroid levels during 12 treatment cycles: No relation to irregular bleedings. *Contraception*, **42**, 423–438.

Jung-Hoffmann, C., Heidt, F. and Kuhl, H. (1988) Effect of two oral contraceptives containing 30 mcg ethinylestradiol and 75 mcg gestodene or 150 mcg desogestrel upon various hormonal parameters. *Contraception*, **38**, 593–603.

Katkam, R.R., Gopalkrishnan, K., Chwalisz, K., Schillinger, E. and Puri, C.P. (1995) Onapristone (ZK 98.299): a potential antiprogestin for endometrial contraception. *Am. J. Obstet. Gynecol.*, **173**, 779–787.

Kazem, R., Messinis, L.E., Fowler, P., Groome, N.P., Knight, P.G. and Templeton, A.A. (1996) Effect of mifepristone (RU486) on the pituitary response to gonadotrophin releasing hormone in women. *Hum. Reprod.*, **11**, 2585–2590.

Kekkonen, R. and Lahteenmaki, P. (1996) Cyclic progestin administration brings about luteinization during continuous antiprogestin treatment. *Contraception*, **53**, 193–195.

Kekkonen, R., Croxatto, H.B., Lahteenmaki, P., Salvatierra, A.M. and Tuominen, J. (1995) Effects of intermittent antiprogestin RU486 combined with cyclic medroxyprogesterone acetate on folliculogenesis and ovulation. *Hum. Reprod.*, **10**, 287–292.

Kettel, L.M., Roseff, S.J., Chiu, T.C., Bangah, M.L., Vale, W., Rivier, J., Burger, H.G. and Yen, S.S. (1991) Follicular arrest during the midfollicular phase of the menstrual cycle: a gonadotropin-releasing hormone antagonist imposed follicular–follicular transition. *J. Clin. Endocrinol. Metab*, **73**, 644–649.

Killick, S.R. (1989) Ovarian follicles during oral contraceptive cycles: Their potential for ovulation. *Fertil. Steril.*, **52**, 580–582.

Killick, S., Eyong, E. and Elstein, M. (1987) Ovarian follicular development in oral contraceptive cycles. *Fertil. Steril.*, **48**, 409–413.

Killick, S.R., Bancroft, K., Oelbaum, S., Morris, J. and Elstein, M. (1990) Extending the duration of the pill-free interval during combined oral contraception. *Adv. Contracept.*, **6**, 33–40.

Killick, S.R., Fitzgerald, C. and Davis, A. (1998) Ovarian activity in women taking an oral contraceptive containing 20 mcg ethinyl estradiol and 150 mcg desogestrel: Effects of low estrogen doses during the hormone-free interval. *Am. J. Obstet. Gynecol.*, **179**, S18–S24.

Kim Bjorklund, T., Landgren, B. and Hamberger, L. (1992) Is the contraceptive effect of 300 mcg of norethisterone mainly peripheral or central? *Contraception*, **45**, 57–66.

Klein, T.A. and Mishell, D.R. (1977) Gonadotropin, prolactin, and steroid hormone levels after discontinuation of oral contraceptives. *Am. J. Obstet. Gynecol.*, **127**, 585–589.

Klitsch, M. (1991) How well do women comply with oral contraceptive regimens? *Fam. Plann. Perspect.*, **23**, 134–136, 138.

Knobil, E. (1980) The neuroendocrine control of the menstrual cycle. *Recent Prog. Horm. Res.*, **36**, 53–88.

Koering, M.J., Danforth, D.R. and Hodgen, G.D. (1991) Early folliculogenesis in primate ovaries: Testing the role of estrogen. *Biol. Reprod.*, **45**, 890–897.

Koering, M.J., Danforth, D.R. and Hodgen, G.D. (1994) Early follicle growth in the juvenile Macaca monkey ovary: The effects of estrogen priming and follicle-stimulating hormone. *Biol. Reprod.*, **50**, 686–694.

Kohler, G., Goretzlehner, G., Rudolf, K., Ruting, M., Meissner, J., Kunkel, S. and Schollberg, K. (1984) The effect of a single midcycle administration of 0.5 or 2.0 mg dienogest (17 alpha-cyanomethyl-17 beta-hydroxy-estra-4, 9-dien-3-one) on pituitary and ovarian function—Investigation for the use as a postcoital contraceptive. *Exp. Clin. Endocrinol.*, **84**, 299–304.

Kuhl, H. (1996) Comparative pharmacology of newer progestogens. *Drugs*, **51**, 188–215.

Kuhl, H., Baziad, A. and Taubert, H.D. (1982) Augmentative and inhibitory effects of chronic steroid injections on LH release and their dependency on time. *Endocrinol. Exp.*, **16**, 93–101.

Kuhl, H., Weber, W., Mehlis, W., Sandow, J. and Taubert, H.D. (1984) Time- and dose-dependent alterations of basal and LH-RH stimulated LH release during treatment with various hormonal contraceptives. *Contraception*, **30**, 467–482.

Kuhl, H., Gahn, G., Romberg, C., Marz, W. and Taubert, H.D. (1985) A randomized cross-over comparison of two low-dose oral contraceptives upon hormonal and metabolic parameters: I. Effects upon sexual hormone levels. *Contraception*, **31**, 583–593.

Kumar, T.C., Shah, R.S., Chitlange, S.M., Hazari, K.T., Gopalkrishnan, K., Vadigoppula, A.D., Vernekar, V.J., Borkar, D.M. and Puri, C.P. (1991) Effects of intranasal administration of norethisterone on folliculogenesis, cervical mucus, vaginal cytology, endometrial morphology and reproductive-endocrine profile in women. *Contraception*, **44**, 245–267.

Landgren, B.M. and Diczfalusy, E. (1980) Hormonal effects of the 300 mcg norethisterone (NET) minipill. 1. Daily steroid levels in 43 subjects during a pretreatment cycle and during the second month of NET administration. *Contraception*, **21**, 87–113.

Landgren, B. and Diczfalusy, E. (1984) Hormonal consequences of missing the pill during the first two days of three consecutive artificial cycles. *Contraception*, **29**, 437–446.

Landgren, B. and Csemiczky, G. (1991) The effect of follicular growth and luteal function of 'missing the pill'. A comparison between a monophasic and a triphasic combined oral contraceptive. *Contraception*, **43**, 149–159.

Landgren, B.M., Balogh, A., Shin, M.W., Lindberg, M. and Diczfalusy, E. (1979) Hormonal effects of the 300 microgram norethisterone (NET) minipill. 2. Daily gonadotrophin levels in 43 subjects during a pretreatment cycle and during the second month of NET administration. *Contraception*, **20**, 585–605.

Landgren, B.M., Lager, S. and Diczfalusy, E. (1981) Hormonal effects of the 300 mcg norethisterone (NET) minipill. 3. Comparison of the short-term (2nd month) and medium-term (6th month) effects in 21 subjects. *Contraception*, **23**, 269–299.

Landgren, B., Dada, O., Aedo, A., Johannisson, E. and Diczfalusy, E. (1990) Pituitary, ovarian and endometrial effects of 300 mcg norethisterone and 30 mcg levonorgestrel administered on cycle days 7 to 10. *Contraception*, **41**, 569–581.

Lasley, B.L., Wang, C.F. and Yen, S.S. (1975) The effects of estrogen and progesterone on the functional capacity of the gonadotrophs. *J. Clin. Endocrinol. Metab.*, **41**, 5–6.

Letterie, G.S. and Chow, G.E. (1992) Effect of 'missed' pills on oral contraceptive effectiveness. *Obstet. Gynecol.*, **79**, 979–982.

Ling, W.Y., Wrixon, W., Zayid, I., Acorn, T., Popat, R. and Wilson, E. (1983) Mode of action of dl-norgestrel and ethinylestradiol combination in postcoital contraception. II. Effect of postovulatory administration on ovarian function and endometrium. *Fertil. Steril.*, **39**, 292–297.

Macklon, N.S. and Fauser, B.C. (2000) Regulation of follicle development and novel approaches to ovarian stimulation for IVF. *Hum. Reprod. Update*, **6**, 307–312.

Magos, A.L., Collins, W.P. and Studd, J.W.W. (1987) Effects of subcutaneous oestradiol implants on ovarian activity. *Br. J. Obstet. Gynaecol.*, **94**, 1192–1198.

Makarainen, L., Van, B.A., Tuomivaara, L., Asplund, B. and Bennink, H.C. (1998) Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. *Fertil. Steril.*, **69**, 714–721.

Mall Haefeli, M., Werner Zodrow, I. and Huber, P.R. (1991) Clinical experiences with Mercilon and Marvelon with particular reference to ovarial function. *Geburtshilfe Frauenheilkd.*, **51**, 34–38.

Marions, L., Danielsson, K.G., Swahn, M.L. and Bygdeman, M. (1998) Contraceptive efficacy of low doses of mifepristone. *Fertil. Steril.*, **70**, 813–816.

Marions, L., Viski, S., Danielsson, K.G., Resch, B.A., Swahn, M.L., Bygdeman, M. and Kovacs, L. (1999) Contraceptive efficacy of daily administration of 0.5 mg mifepristone. *Hum. Reprod.*, **14**, 2788–2790.

Messinis, I.E., Krishnan, M., Kazem, R., Khadilkar, S. and Templeton, A.A. (1997) Effect of mifepristone on folliculogenesis in women treated with recombinant FSH. *Clin. Endocrinol.*, **46**, 309–314.

Molloy, B.G., Coulson, K.A., Lee, J.M. and Watters, J.K. (1985) 'Missed pill' conception: fact or fiction? *Br. Med. J.* , **290**, 1474–1475.

Nuttall, I.D., Elstein, M. and Fahmy, D.R. (1982) The effect of norethisterone capsules on the pituitary–ovarian axis. *Contraception*, **25**, 51–57.

Pache, T.D., Wladimiroff, J.W., De Jong, F.H., Hop, W.C. and Fauser, B.C.J.M. (1990) Growth patterns of nondominant ovarian follicles during the normal menstrual cycle. *Fertil. Steril.*, **54**, 638–642.

Paltieli, Y., Eibschitz, I., Ziskind, G., Ohel, G., Silbermann, M. and Weichselbaum, A. (2000) High progesterone levels and ciliary dysfunction—a possible cause of ectopic pregnancy. *J. Assist. Reprod. Genet.*, **17**, 103–106.

Perez-Lopez, F.R., L'Hermite, M. and Robyn, C. (1975) Gonadotrophin hormone releasing tests in women receiving hormonal contraception. *Clin. Endocrinol. Oxf.*, **4**, 477–485.

Pincus, G., Rock, J., Garcia, C.R., Rice Whira, E., Pamaqua, M. and Rodriques, I. (1958) Fertility control with oral medication. *Am. J. Obstet. Gynecol.*, **75**, 1333–1346.

Rabe, T., Nitsche, D.C. and Runnebaum, B. (1997) The effects of monophasic and triphasic oral contraceptives on ovarian function and endometrial thickness. *Eur. J. Contracept. Reprod. Health Care*, **2**, 39–51.

Rice, C., Killick, S., Hickling, D. and Coelingh Bennink, H.J.T. (1996) Ovarian activity and vaginal bleeding patterns with a desogestrel-only preparation at three different doses. *Hum. Reprod.*, **11**, 737–740.

Rommler, A., Baumgarten, S., Schwartz, U. and Hammerstein, J. (1982) Anti-estrogenic effects of contraceptive progestins on the dynamics of gonadotropin release. *Contraception*, **25**, 619–627.

Rommler, A., Baumgarten, S., Moltz, L., Schwartz, U. and Hammerstein, J. (1985) Oral contraceptives and pituitary response to GnRH: comparative study of progestin-related effects. *Contraception*, **31**, 295–303.

Rubinstein, L., Moguilevsky, J. and Leiderman, S. (1978) The effect of oral contraceptives on the gonadotropin response to LHRH. *Obstet. Gynecol.*, **52**, 571–574.

Sanchez-Criado, J.E., Bellido, C., Tebar, M., Ruiz, A. and Gonzalez, D. (1999) The antiprogestin RU486 dissociates LH and FSH secretion in male rats: evidence for direct action at the pituitary level. *J. Endocrinol.*, **160**, 197–203.

Schally, A.V., Parlow, A.F., Carter, W.H., Saito, M., Bowers, C.Y. and Arimura, A. (1970) Studies on the site of action of oral contraceptive steroids. II. Plasma LH and FSH levels after administration of antifertility steroids and LH-releasing hormone (LH-RH). *Endocrinology*, **86**, 530–541.

Schoot, D.C., Bennink, H.J.T.C., Mannaerts, B.M.J.L., Lamberts, S.W.J., Bouchard, P. and Fauser, B.C.J.M. (1992) Human recombinant follicle-stimulating hormone induces growth of preovulatory follicles without concomitant increase in androgen and estrogen biosynthesis in a woman with isolated gonadotropin deficiency. *J. Clin. Endocrinol. Metab.*, **74**, 1471–1473.

Schubert, W. and Cullberg, G. (1987) Ovulation inhibition with 17 beta-estradiol cyclo-octyl acetate and desogestrel. *Acta Obstet. Gynecol. Scand.*, **66**, 543–547.

Scott, J.A., Brenner, P.F., Kletzky, O.A. and Mishell, D.R. (1978a) Factors affecting pituitary gonadotropin function in users of oral contraceptive steroids. *Am. J. Obstet. Gynecol.*, **130**, 817–821.

Scott, J.Z., Kletzky, O.A., Brenner, P.F. and Mishell, D.R. Jr (1978b) Comparison of the effects of contraceptive steroid formulations containing two doses of estrogen on pituitary function. *Fertil. Steril.*, **30**, 141–145.

Shaaban, M.M., El Nashar, I.M., Ghaneimah, S.A., Gomaa, A.A., Salah, M. and Abdel-Aleem, A.M. (1984) Hormonal changes during the first year of use of subdermal levonorgestrel implants, Norplant. *Contraception*, **30**, 391–405.

Shaaban, M.M., Segal, S., Salem, H.T., Ghaneimah, S.A., Khalifa, E. and Ahmed, A. (1993) Sonographic assessment of ovarian and endometrial changes during long-term Norplant use and their correlation with hormonal levels. *Fertil. Steril.*, **59**, 998–1002.

Shah, R.S., Toddywalla, V., Maskati, B.T., Desai, A.D., Karnik, P.P., David, G.F. and Anand Kumar, T.C. (1985) Reproductive endocrine effects of intranasal administration of norethisterone (net) to women. *Contraception*, **32**, 135–147.

Shaw, G., Killick, S. and Elstein, M. (1992) Assessment of ovarian activity in a gestodene containing triphasic oral contraceptive. *Br. J. Fam. Plann.*, **18**, 76–78.

Shoupe, D., Horenstein, J., Mishell, D.R., Lacarra, M. and Medearis, A. (1991) Characteristics of ovarian follicular development in Norplant users. *Fertil. Steril.*, **55**, 766–770.

Slayden, O.D., Zelinski-Wooten, M.B., Chwalisz, K., Stouffer, R.L. and Brenner, R.M. (1998) Chronic treatment of cycling rhesus monkeys with low doses of the antiprogestin ZK 137 316: morphometric assessment of the uterus and oviduct. *Hum. Reprod.*, **13**, 269–277.

Smith, S.K., Kirkman, R.J.E., Arce, B.B., McNeilly, A.S., Loudon, N.B. and Baird, D.T. (1986) The effect of deliberate omission of Trinordiol registered or Microgynon registered on the hypothalamo-pituitary–ovarian axis. *Contraception*, **34**, 513–522.

Somkuti, S.G., Sun, J., Yowell, C.W., Fritz, M.A. and Lessey, B.A. (1996) The effect of oral contraceptive pills on markers of endometrial receptivity. *Fertil. Steril.*, **65**, 484–488.

Song, J.Y. and Fraser, I.S. (1995) Effects of progestogens on human endometrium. *Obstet. Gynecol. Surv.*, **50**, 385–394.

Song, S., Chen, J., Lu, C., Yang, P., Yang, Q., Fan, B., He, M., Gui, Y., Li, L. and Fotherby, K. (1993) Effects of different doses of norethisterone on ovarian function, serum sex hormone binding globulin and high density lipoprotein-cholesterol. *Contraception*, **47**, 527–537.

Spellacy, W.N., Kalra, P.S., Buhi, W.C. and Birk, S.A. (1980) Pituitary and ovarian responsiveness to a graded gonadotropin releasing factor stimulation test in women using a low-estrogen or a regular type of oral contraceptive. *Am. J. Obstet. Gynecol.*, **137**, 109–115.

Spitz, I.M., Croxatto, H.B., Salvatierra, A.M. and Heikinheimo, O. (1993) Response to intermittent RU486 in women. *Fertil. Steril.*, **59**, 971–975.

Spitz, I.M., Croxatto, H.B. and Robbins, A. (1996) Antiprogestins: mechanism of action and contraceptive potential. *Ann. Rev. Pharmacol. Toxicol.*, **36**, 47–81.

Spitz, I.M., Van Look, P.F. and Coelingh Bennink, H.J. (2000) The use of progesterone antagonists and progesterone receptor modulators in contraception. *Steroids*, **65**, 817–823.

Spona, J., Elstein, M., Feichtinger, W., Sullivan, H., Ludicke, F., Muller, U. and Dusterberg, B. (1996a) Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception*, **54**, 71–77.

Spona, J., Feichtinger, W., Kindermann, C., Wunsch, C. and Brill, K. (1996b) Inhibition of ovulation by an oral contraceptive containing 100 mcg levonorgestrel in combination with 20 mcg ethinylestradiol. *Contraception*, **54**, 299–304.

Stratton, P., Hartog, B., Hajizadeh, N., Piquion, J., Sutherland, D., Merino, M., Lee, Y.J. and Nieman, L.K. (2000) A single mid-follicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women. *Hum. Reprod.*, **15**, 1092–1099.

Sullivan, H., Furniss, H., Spona, J. and Elstein, M. (1999) Effect of 21-day and 24-day oral contraceptive regimens containing gestodene (60 mcg) and ethinyl estradiol (15 mcg) on ovarian activity. *Fertil. Steril.*, **72**, 115–120.

Swahn, M.L., Danielsson, K.G. and Bygdeman, M. (1996) Contraception with anti-progesterone. *Baillieres Clin. Obstet. Gynaecol.*, **10**, 43–53.

Tafurt, C.A., Sobrevilla, L.A. and De Estrada, R. (1980) Effects of progestin-estrogen combination and progestational contraceptives on pituitary gonadotropins, gonadal steroids, and sex hormone-binding globulin. *Fertil. Steril.*, **33**, 261–266.

Task Force on Postovulatory Methods of Fertility Regulation (1999) Comparison of three single doses of mifepristone as emergency contraception: A randomised trial. *Lancet*, **353**, 697–702.

Tayob, Y., Adams, J., Jacobs, H.S. and Guillebaud, J. (1985) Ultrasound

demonstration of increased frequency of functional ovarian cysts in women using progestogen-only oral contraception. *Br. J. Obstet. Gynaecol.*, **92**, 1003–1009.

Tayob, Y., Guillebaud, J., Adams, J. and Jacobs, H.S. (1986) Studies on ovarian function in users of the progestagen only contraceptive pill. *J. Obstet. Gynecol.*, **6**, S91–S95.

Tayob, Y., Robinson, G., Adams, J., Nye, M., Whitelaw, N., Shaw, R.W., Jacobs, H.S. and Guillebaud, J. (1990) Ultrasound appearance of the ovaries during the pill-free interval. *Br. J. Fam. Plann.*, **16**, 94–96.

Teichmann, A.T., Brill, K., Albring, M., Schnitker, J., Wojtynek, P. and Kustra, E. (1995) The influence of the dose of ethinylestradiol in oral contraceptives on follicle growth. *Gynecol. Endocrinol.*, **9**, 299–305.

Thom, M.H., Collins, W.P. and Studd, J.W. (1981) Hormonal profiles in postmenopausal women after therapy with subcutaneous implants. *Br. J. Obstet. Gynaecol.*, **88**, 426–433.

Thomas, K. and Vankrieken, L. (1990) Inhibition of ovulation by low-dose monophase contraceptive containing gestodene. *Am. J. Obstet. Gynecol.*, **163**, 1404–1410.

Trussell, J. and Kost, K. (1987) Contraceptive failure in the United States: a critical review of the literature. *Stud. Fam. Plann.*, **18**, 237–283.

Vallon, A.M., Cristol, P., Hedon, B., Deschamps, F., Plauchut, A., Taillant, M. and Pizelle, A.M. (1992) Ovarian suppressive activity of a low dose monophasic oral contraceptive during correct and incorrect pill intake. *Contracept. Fertil. Sex.*, **20**, 521–529.

Van der Does, J., Exalto, N., Dieben, T. and Coelingh Bennink, H.J.T. (1995) Ovarian activity suppression by two different low-dose triphasic oral contraceptives. *Contraception*, **52**, 357–361.

van der Vange, N., Bruinse, H.W., Coelingh Bennink, H.J.T. *et al.* (1986) Effects of seven low dose combined oral contraceptives on ovarian function, measured by ultrasound examination and peripheral endocrine parameters. In van der Vange, N. (ed.) *Seven Low-Dose Oral Contraceptives and their Influence on Metabolic Pathways and Ovarian Activity.* Dissertation, Utrecht, pp. 71–84.

Van Heusden, A.M. and Fauser, B.C.J.M. (1996) FSH and ovarian function during combined oral contraceptive regimens. In Fauser, B.C.J.M. (ed.) *FSH Action and Intraovarian Regulation.* The Parthenon Publishing Group, London, UK, pp. 211–221.

Van Heusden, A.M. and Fauser, B.C.J.M. (1999) Activity of the pituitary–ovarian axis in the pill-free interval during use of low-dose combined oral contraceptives. *Contraception*, **59**, 237–243.

Van Heusden, A.M., Killick, S.R., Coelingh Bennink, H.J. and Fauser, B.C.J.M. (2000) Single monthly administration of the anti-progestagen Org 31710 in users of the 75 microg desogestrel progestagen-only pill: effects on pituitary–ovarian activity. *Hum. Reprod.*, **15**, 629–636.

Van Heusden, A.M., Coelingh Bennink, H.J. and Fauser, B.C.J.M. (2002) FSH and ovarian response: spontaneous recovery of pituitary–ovarian activity during the pill-free period vs. exogenous recombinant FSH during high-dose combined oral contraceptives. *Clin. Endocrinol. (Oxf.)*, **56**, 509–517.

van Santbrink, E.J., Hop, W.C., van Dessel, H.J., De Jong, F.H. and Fauser, B.C.J.M. (1995) Decremental follicle-stimulating hormone and dominant follicle development during the normal menstrual cycle. *Fertil. Steril.*, **64**, 37–43.

Van Uem, J.F.H.M., Hsiu, J.G., Chillik, C.F., Danforth, D.R., Ulmann, A., Baulieu, E.E. and Hodgen, G.D. (1989) Contraceptive potential of RU 486 by ovulation inhibition: I. Pituitary versus ovarian action with blockade of estrogen-induced endometrial proliferation. *Contraception*, **40**, 171–184.

Wang, C.F., Lasley, B.L., Lein, A. and Yen, S.S. (1976) The functional changes of the pituitary gonadotrophs during the menstrual cycle. *J. Clin. Endocrinol. Metab.*, **42**, 718–728.

Wang, E., Shi, S., Cekan, S.Z., Landgren, B.M. and Diczfalusy, E. (1982) Hormonal consequences of 'missing the pill'. *Contraception*, **26**, 545–566.

Watson, N.R., Studd, J.W.W., Riddle, A.F. and Savvas, M. (1988) Suppression of ovulation by transdermal oestradiol patches. *Br. Med. J.*, **297**, 900–901.

Wenzl, R., Bennink, H.C., Van Beek, A., Spona, J. and Huber, J. (1993) Ovulation inhibition with a combined oral contraceptive containing 1 mg micronized 17 beta-estradiol. *Fertil. Steril.*, **60**, 616–619.

Westcombe, R., Ellis, R. and Fotherby, K. (1988) Suppression of ovulation in women using a triphasic oral contraceptive. *Br. J. Fam. Plann.*, **13**, 127–132.

Wildt, L., Hausler, A., Marshall, G., Hutchison, J.S., Plant, T.M., Belchetz, P.E. and Knobil, E. (1981a) Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. *Endocrinology*, **109**, 376–385.

Wildt, L., Hutchison, J.S., Marshall, G., Pohl, C.R. and Knobil, E. (1981b) On the site of action of progesterone in the blockade of the estradiol-induced gonadotropin discharge in the rhesus monkey. *Endocrinology*, **109**, 1293–1294.

Wolf, J.P., Danforth, D.R., Ulmann, A., Baulieu, E.E. and Hodgen, G.D. (1989) Contraceptive potential of RU 486 by ovulation inhibition: II. Suppression of pituitary gonadotropin secretion *in vitro*. *Contraception*, **40**, 185–193.

Wu, S., Wang, C. and Wang, Y. (1999) A randomized, double-blind, multicentre study on comparing levonorgestrel and mifepristone for emergency contraception. *Zhonghua Fu Chan Ke. Za Zhi.*, **34**, 327–330.

Yen, S.S. and Tsai, C.C. (1971) The biphasic pattern in the feedback action of ethinyl estradiol on the release of pituitary FSH and LH. *J. Clin. Endocrinol. Metab.*, **33**, 882–887.

Yen, S.S., Vandenberg, G., Rebar, R. and Ehara, Y. (1972) Variation of pituitary responsiveness to synthetic LRF during different phases of the menstrual cycle. *J. Clin. Endocrinol. Metab.*, **35**, 931–934.

Young, R.L., Snabes, M.C., Frank, M.L. and Reilly, M. (1992) A randomized, double-blind, placebo-controlled comparison of the impact of low-dose and triphasic oral contraceptives on follicular development. *Am. J. Obstet. Gynecol.*, **167**, 678–682.

Zelinski-Wooten, M.B., Slayden, O.D., Chwalisz, K., Hess, D.L., Brenner, R.M. and Stouffer, R.L. (1998) Chronic treatment of female rhesus monkeys with low doses of the antiprogestin ZK 137 316: establishment of a regimen that permits normal menstrual cyclicity. *Hum. Reprod.*, **13**, 259–267.