

Ovulation incidence with oral contraceptives: a literature review

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Abstract

Background and methodology Combined oral contraceptives (COCs) provide reliable and convenient contraception, although contraindications and tolerability issues may limit their use in some women. Progestogen-only pills (POPs) may be more suitable for some women, however, traditional POPs do not have the same contraceptive efficacy as COCs. A literature search was performed in order to assess the incidence of ovulation with available COCs, traditional POPs and with a desogestrel POP [Cerazette®, 75 µg desogestrel (DSG)]. The following databases were searched: MEDLINE, EMBASE, Biosis, Derwent Drug File, Current Contents and the in-house Organon database 'Docs' (which contains all published reports of Organon products). Searches used free-text terms [e.g. Contraceptive\$ in combination with (Ovulat\$ adj Rate\$), (Ovar\$ adj Activ\$) or (Escap\$ adj Ovulat\$)] and were limited to the search criteria 'Human' and 'from 1979 onwards'. The searches included publications up to July 2008.

Results Many of the studies were hampered by inadequate ovulation criteria; however, the overall incidence of ovulation determined by the reports uncovered in the literature search was 2.0% [95% confidence interval (CI) 1.1–3.3] with COCs containing 30–35 µg ethinylestradiol (EE), 1.1% (95% CI 0.60–2.0) with 15–20 µg EE COCs, 4.6% (95% CI 2.8–6.9) with phasic COCs, 1.25% (95% CI 0.03–6.8) with Cerazette and 42.6% (95% CI 33.4–52.2) with traditional POPs.

Conclusions The findings indicate that COCs and the desogestrel POP are equally effective in suppressing ovulation, whilst the traditional POP formulations are less effective.

Keywords combined oral contraceptive, desogestrel, oral contraceptive, ovulation, progestogen-only pill

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Introduction

Oral contraceptives are the most common means of contraception in many countries and it is estimated that as many as 100 million women worldwide currently rely on this method. Approximately half of all married women in Western Europe use the oral contraceptive pill (i.e. three in every five contraceptive users) and, in the USA, they have been used by 80% of all women born since 1945.^{1–4} Their widespread use warrants continuing efforts to improve and refine oral contraceptive methods.

The first oral contraceptive pill became available in 1960 and consisted of 150 µg mestranol plus 9.85 mg norethynodrel. These doses were much higher for both the estrogenic component and the progestogenic component compared to modern low-dose combined oral contraceptives (COCs). COCs provide highly reliable and convenient contraception, which is safe and well tolerated by many women. A number of side effects predominantly attributed to estrogen, such as nausea, headache, breast-tenderness and bloating, can, however, make them unacceptable to some women. These problems have been addressed to some extent by lowering the doses of both estrogen and progestogen.

Estrogen-free contraception appeared in the early 1970s when the traditional progestogen-only pills (POPs) were developed in response to reports of the effects of estrogen on thromboembolic disease. As well as lacking the estrogen

Key message points

- Many contraceptive ovulation inhibition studies are hampered by inadequate methodology and/or ovulation criteria.
- Combined oral contraceptives and the desogestrel progestogen-only pill (POP) are equally effective in suppressing ovulation, and more effective than traditional POP formulations.

component, they also contain lower doses of progestogen than COCs. In contrast to COCs, which are not recommended for breastfeeding women as they can impair the quality and quantity of breast milk,⁵ POPs are suitable for breastfeeding women also. However, traditional POPs are also associated with a number of significant disadvantages. Most importantly, they lack the efficacy of the COCs with regard to ovulation inhibition (ovulation inhibition has been reported to occur in only approximately 50% of the treatment periods with traditional POPs).⁶ Contraceptive efficacy with traditional POPs places greater reliance on an increased viscosity of the cervical mucus that reduces sperm viability and penetration.⁷ This effect is extremely sensitive to progestogen levels in the serum.⁸ The efficacy of traditional POPs therefore requires strict adherence to the dosing schedule (i.e. efficacy is significantly diminished if the pill is taken more than 3 hours later than scheduled). Other effects – such as reduction in the activity of the cilia in the Fallopian tubes and changes in the endometrium that make implantation unfavourable – also play some role.⁶

Cerazette® is a POP that contains 75 µg desogestrel (DSG). Because DSG, which is rapidly converted to its active metabolite, etonogestrel^{9,10} is more potent than historical POP progestogens and is more selective with regard to androgen receptors,¹¹ it can be used at doses sufficient to inhibit ovulation whilst avoiding androgenic effects. Thus, the primary mode of action is ovulation inhibition, and the effects that traditional POPs depend

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upon are secondary for the DSG POP. Increased viscosity of the cervical mucus, as with traditional POPs, provides additional contraceptive protection. The DSG POP has been shown to result in a consistently low Insler score (<9) in the majority of women,¹² which indicates hostility to sperm penetration, as well as having effects on the endometrium that make it unsuitable to support the fertilised ovum. Moreover, while mucus impenetrability is generally considered to be lost approximately 27 hours after dosing,⁶ ovulation inhibition is a more robust mechanism. For the DSG POP, the effects of both ovulation inhibition and cervical mucus impenetrability are considered to provide much longer contraceptive efficacy, allowing a 12-hour pill intake window comparable to that used with COCs.¹³

In order to assess the incidence of ovulation with available COCs and POPs, and to compare this with the ovulation rate reported with the DSG POP, a literature review was performed.

Methods

A literature search was performed in the following databases: MEDLINE, EMBASE, Biosis, Derwent Drug File, Current Contents and the in-house Organon database 'Docs'. This in-house database consists of all publications extracted from the previously mentioned databases plus the Japanese database JICST, as well as congress abstracts and CD-ROMs. Searches were performed with free-text terms [e.g. Contraceptive\$ in combination with (Ovulat\$ adj Rate\$), (Ovar\$ adj Activ\$) or (Escap\$ adj Ovulat\$)] and were limited to the search criteria 'Human' and 'from 1979 onwards'. The searches included publications up to July 2008. Reference lists in publications found via the literature search were also screened for additional publications.

Many of the studies identified in the literature search did not fulfil the criteria for the determination of ovulation as defined by Landgren and Diczfalusy (i.e. progesterone levels of >16 nmol/l sustained for at least 5 days)^{14,15} and in many cases no measurements were performed during the most critical days for escape ovulation. The ovulation rates reported in all the studies have been included in Tables 1–4 in order to provide a more complete picture of the data available. However, only data from studies using the strictest criteria for determination of ovulation should be considered as providing accurate information about the incidence of ovulation with the various oral contraceptive methods.

Reported ovulation rates were grouped according to the oral contraceptive method used: COCs containing 30–35 µg ethinylestradiol (EE), COCs containing 15–20 µg EE, phasic COCs, and POPs. The ovulation rate is expressed as the percentage of subjects experiencing ovulation out of the total number of subjects studied; 95% confidence intervals (CIs) were calculated using exact binomial distribution.¹⁶

Results

COCs containing 30–35 µg EE

Studies employing COCs containing 30–35 µg EE are shown in Table 1,^{17–37} the majority of which reported an absence of ovulation. A total of 16 out of 791 (2.0%) subjects were found to ovulate. Differences between the various types of COC were observed, with the ovulation incidence ranging from 1% to 30%. The upper limits of the 95% CIs also varied widely between the studies, ranging from 1.7% to 65.2%. The most widely studied combinations were levonorgestrel (LNG)/EE (273 subjects in 10 studies) with an ovulation incidence of 2.2% and gestodene (GSD)/EE (277 subjects in four studies) with an ovulation incidence of 0%.

Only four studies used a progesterone level of >16 nmol/l as the criterion for ovulation. One of these studies, conducted over six cycles, identified one ovulation amongst 10 users of cyproterone acetate (CPA)/EE 2000/35 µg, but none in 10 users of LNG/EE 150/30 µg, 10 users of DSG/EE 150/30 µg or 10 users of norethisterone (NET)/EE 1000/35 µg.¹⁸ Progesterone levels were measured every 4 days during Cycles 1, 3 and 6. The other three studies all assessed the effects of deliberate omission of pill intake. Landgren and Csemiczky³² observed one ovulation in 10 subjects using DSG/EE 150/30 µg after a deliberate extension of the preceding pill-free interval to 10 days. Progesterone levels were measured every other day. No ovulations were reported in 10 women after the omission of LNG/EE 150/30 µg for the first 2 days of three consecutive cycles.²⁰ Progesterone was measured three times weekly during 90 days. Similarly, missing two doses of LNG/EE 150/30 µg in one cycle did not result in ovulation in 31 women in whom progesterone levels were measured daily.²¹

Amongst the studies that used different progesterone levels to define ovulation, Spona *et al.*³⁰ reported no ovulation (progesterone >5 nmol/l) in 22 women using dienogest (DNG)/EE 2000/30 µg, and Elomaa *et al.*²³ found no ovulation (progesterone >9.6 nmol/l) among 34 women using GSD/EE 75/30 µg. Kuhl *et al.*³³ reported one ovulation (progesterone >9.6 nmol/l) among 11 subjects during one observed cycle of DSG/EE 150/30 µg and two ovulations during LNG/EE 150/30 µg. Among 85 women who started norgestrel (NG)/EE 300/30 µg on Day 1, 4 or 7 of their menstrual cycle, three (2.4%) ovulated (progesterone >9.6 nmol/l) during one monitored cycle.³⁶ Birch *et al.*³⁷ observed ovulation in one woman out of eight on LNG/EE 150/30 µg for three cycles, using ultrasound evidence of corpus luteum formation as the ovulatory criterion, but the associated hormone levels were extremely low (progesterone 2.5 nmol/l).

The remaining studies used a variety of other criteria to assess ovulation. In the largest study ($n = 209$)²⁴ ultrasound measurements were scheduled during Days 18–21 of the cycle, which is considered the least critical period with respect to escape ovulation. Despite substantial follicular growth (maximum follicular diameter >10 mm in >10% of cycles), no ruptured follicles were observed and an absence of escape ovulation was therefore claimed. The fact that a pregnancy occurred illustrates the shortcomings of this ultrasound-only approach. A number of studies either did not assess progesterone levels,²⁶ had no predefined definition of ovulation,^{19,22,25,29,31} or did not perform measurements during the most critical days for escape ovulation.^{17,25,27,28,35}

COCs containing 15–20 µg EE

Table 2 shows the studies that have been conducted with COCs containing 15–20 µg EE.^{17,23,24,26,38–55} Overall, 12 out of 1030 (1.1%) subjects were found to have ovulated. Differences between the various types of COCs were observed, with the ovulation incidence ranging from 0.0% to 8.6%. The upper limits of the 95% CIs also varied widely between studies, ranging from 1.7% to 49.4%. DSG/EE 150/20 µg (507 subjects in 10 studies) and GSD/EE (209 subjects in seven studies) were the most commonly investigated combinations, with ovulation rates of 0.2% and 0.0%, respectively.

None of the studies used a progesterone level of >16 nmol/l to define ovulation. One study reported ovulation, using both ultrasound and serum progesterone level (>5 nmol/l), in 2/25 subjects during three cycles of LNG/EE 100/20 µg.³⁸ Application of the progesterone >16 nmol/l

Table 1 Ovulation in studies with combined oral contraceptives containing 30–35 µg ethinylestradiol

Reference	Progestogen/EE µg/µg	Duration Schedule for determination of ovulation (cycles)	Ovulation criteria		Ovulation occurrence (subjects)	Ovulation rate	
			P (nmol/l)	US		%	95% CI
						LL	UL
Vange ¹⁸	LNG/EE 150/30	6	16.0	Rupture	0/10	0.0	30.8
Landgren ²⁰	LNG/EE 150/30 (PFI 9 days)	3	16.0	ND	0/10	0.0	30.8
Wang ²¹	LNG/EE 150/30 (2 miss)	1	16.0	ND	0/31	0.0	11.2
Kuhl ³³	LNG/EE 150/30	3	9.6	ND	2/11	18.2	51.8
Schwartz ³⁶	NG/EE 300/30 (Day 1 start)	1	9.6	13 mm (NA)	2/29	6.9	22.8
	NG/EE 300/30 (Day 4 start)				1/29	3.5	17.8
	NG/EE 300/30 (Day 7 start)				0/27	0.0	12.8
Smith ¹⁹	LNG/EE 150/30 (21 days)	<1	NPD	ND	0/6	0.0	45.9
Morris ²²	LNG/EE 150/30 (1 miss)	1	NPD	ND	0/10	0.0	30.8
Duijkers ³¹	LNG/EE 150/30	2	NPD	NPD	0/19	0.0	17.6
Rabe ¹⁷	LNG/EE 150/30	1	4.5	NA	0/83	0.0	4.3
Birtch ³⁷	LNG/EE 150/30	3	NPD	15 mm, CL next day	1/8	12.5	52.7
All	LNG/EE 150/30				6/273	2.2	4.7
Elomaa ²³	GSD/EE 75/30	2	9.6	NA	0/34	0.0	10.3
Teichmann ²⁴	GSD/EE 75/30	9	ND	Rupture	0/209	0.0	1.7
Thomas ²⁵	GSD/EE 75/30	6	NPD	NPD	0/18	0.0	18.5
Rabe ¹⁷	GSD/EE 75/30	1	4.5	NA	0/16	0.0	20.6
All	GSD/EE 150/30				0/277	0.0	1.3
Vange ¹⁸	DSG/EE 150/30	6	16.0	Rupture	0/10	0.0	30.8
Landgren ³²	DSG/EE 150/30 (PFI 10 days)	1	16.0	NA	1/10	10.0	44.5
Kuhl ³³	DSG/EE 150/30	3	9.6	ND	1/11	9.1	41.3
Heusden ²⁶	DSG/EE 150/30	2	ND	NPD	0/12	0.0	26.5
Rabe ¹⁷	DGS/EE 150/30	1	4.5	NA	0/59	0.0	6.1
Dericks-Tan ²⁷	DSG/EE 150/30	1	9.6	ND	0/8	0.0	36.9
All	DSG/EE 150/30				1/100	1.0	5.4
Vange ¹⁸	NET/EE 1000/35	6	16.0	Rupture	0/10	0.0	30.8
Grimes ²⁸	NET/EE 1000/35	6	9.6	NA	0/10	0.0	30.8
Chowdhury ³⁴	NETA/EE 1000/30	1	12.8	ND	1/10	10.0	44.5
	<i>idem</i> , 2 miss pills Cycle 1				10/35	28.6	46.3
	<i>idem</i> , 2 miss pills Cycle 4				5/19	26.3	51.2
All	NET(A)/EE 1000/30				1/30	3.3	17.2
Hédon ²⁹	NGM/EE 250/35	1	NPD	NPD	0/5	0.0	52.2
Rabe ¹⁷	NGM/EE 250/35	1	4.5	NA	0/33	0.0	10.6
Birtch ³⁷	NGM/EE 250/35	3	NPD	15 mm, CL next day	1/8	12.5	52.7
All	NGM/EE 250/35				1/46	2.2	11.5
Vange ¹⁸	CPA/EE 2000/35	6	16.0	Rupture	1/10	10.0	44.5
Spona ³⁰	DNG/EE 2000/30	3	5.0	Rupture	0/22	0.0	15.4
Grimes ²⁸	NET/EE 500/35	6	9.6	NA	3/10	30.0	65.2
Rosenbaum ³⁵	DSP/EE 2000/30	3	5.0	Rupture	3/23	13.0	33.6
All 30–35 µg EE OCs					16/791	2.0	3.3

Values resulting from studies with scheduled omissions in tablet intake (in italics) were not included in the calculation of totals. CI, confidence interval; CL, corpus luteum; COC, combined oral contraceptive; CPA, cyproterone acetate; DNG, dienogest; DSG, desogestrel; DSP, drospirenone; EE, ethinylestradiol; GSD, gestodene; LL, lower limit; LNG, levonorgestrel; NA, not applied for ovulation assessment; ND, not done; NET, norethisterone; NETA, norethisterone acetate; NG, norgestrel; NGM, norgestimate; NPD, not predefined; P, progesterone; PFI, pill-free interval; UL, upper limit; US, ultrasound.

Table 2 Ovulation in studies with combined oral contraceptives containing 15–20 µg ethinylestradiol

Reference	Progestogen/EE µg/µg	Duration (cycles)	Schedule for determination of ovulation	Ovulation criteria		Ovulation occurrence (subjects)	Ovulation rate		
				P (nmol/l)	US		%	95% CI	
				LL	UL				
Coney ³⁸	LNG/EE 100/20	3	Cycles 1, 2, 3: 3 times/week	5.0	>13 mm, rupture	2/25	8.0	1.0	26.0
Spona ³⁹	LNG/EE 100/20	3	Cycles 1, 2, 3: every 2 days	5.0	>13 mm, rupture	0/24	0.0	0.0	14.2
Creinin ⁴³	LNG/EE 100/20 (PFI 9 days)	2	Cycle 2: Days 10, 14, 21, 28	9.6	NPD	4/35	11.4	3.2	26.7
Koch ⁴⁰	LNG/EE 100/20	3	Cycles 1, 2, 3: Days 1, 7, 14, 20	5.0	>13 mm, rupture	0/18	0.0	0.0	18.5
Teichmann ⁴¹	LNG/EE 100/20	3	Cycles 1, 2, 3: Days 1, 3, 7, 11, 15, 19	9.6	Rupture	0/13	0.0	0.0	24.7
Pierson ⁴²	LNG/EE 100/20	3	Cycle 1: every 2 days; Cycle 2: weekly; Cycle 3: every 3 days (US); P once, when indicated by US	9.6	Rupture	7/25	28.0	12.1	49.4
All	LNG/EE 100/20					9/105	8.6	4.0	15.6
Spona ⁴⁵	GSD/EE 75/20 (21/7) GSD/EE 75/20 (23/5)	3	Cycles 1, 2, 3: every 2 days	5.0	>13 mm, rupture	0/30	0.0	0.0	11.6
Fitzgerald ⁴⁷	GSD/EE 75/20	3	Cycles 1, 2, 3: Days 2, 4, 8, 10; Days 11–18 daily; Days 20, 25, 28	5.0	50%↓, <24 hours	0/19	0.0	0.0	17.6
Archer ⁴⁴	GSD/EE 75/20	3	Cycles 1, 2, 3: Days 14, 16, 18, 22 (P); Days 1, 3, 7, 11, 15, 19 (US)	9.6	>16 mm	0/38	0.0	0.0	9.3
Heusden ²⁶	GSD/EE 75/20	2	Cycle 2: daily during PFI (Days 22–28)	ND	NPD	0/15	0.0	0.0	21.8
Heusden ⁴⁶	GSD/EE 75/20	6	Cycles 3, 6: Days 1, 2, 5, 10, 21	NPD	ND	0/67	0.0	0.0	5.4
Fitzgerald ⁴⁸	GSD/EE 75/20	3	Cycles 1, 2, 3: Days 2, 4, 8, 10, 12, 14, 16, 18, 20, 25, 28	NPD	NPD	0/26	0.0	0.0	13.2
Crosignani ⁴⁹	GSD/EE 75/20	8	Cycle 3 or 4, 6, 7 or 8: 2 times between Day 7–13 and Days 16–20	NPD	NPD	0/14	0.0	0.0	23.2
All	GSD/EE 75/20					0/209	0.0	0.0	1.7
Elomaa ²³	DSG/EE 150/20	2	Cycle 2: Days 1, 2, 3, 5, 7, 26, 28	9.6	NA	0/31	0.0	0.0	11.2
Fitzgerald ⁴⁶	DSG/EE 150/20	3	Cycles 1, 2, 3: Days 2, 4, 8, 10; Days 11–18 daily; Days 20, 25, 28	5.0	50%↓, <24 hours	0/19	0.0	0.0	17.6
Pfrunders ⁵²	DSG/EE 150/20	1	Cycle 1: Days 11 or 12 (US) and 23 (P)	4.9	>12 mm	0/18	0.0	0.0	18.5
Teichmann ²⁴	DSG/EE 150/20	9	Cycles 1, 3, 6, 9: daily during Days 18–21 (US)	ND	Rupture	0/209	0.0	0.0	1.7
Heusden ²⁶	DSG/EE 150/20	2	Cycle 2: daily during PFI (Days 22–28)	ND	NPD	0/17	0.0	0.0	19.5
Heusden ⁴⁶	DSG/EE 150/20	6	Cycles 3, 6: Days 1, 2, 5, 10, 21	NPD	ND	0/69	0.0	0.0	5.2
Crosignani ⁴⁹	DSG/EE 150/20	8	Cycle 3 or 4, 6, 7 or 8: 2 times between Days 7–13 and Days 16–20	NPD	NPD	0/15	0.0	0.0	21.8
Killick ⁵³	DSG/EE 150/20	3	Cycles 1, 2, 3: 2 times/week	NPD	>15 mm, rupture	1/23	4.4	0.1	21.9
Rabe ¹⁷	DSG/EE 150/20	1	Cycle 1: once between Days 10–12 and Days 16–18	4.5	NA	0/47	0.0	0.0	7.5
Rossmann ⁵¹	DSG/EE 150/20	3	Cycle 1, 2, 3: Days 6, 7, 8, if activity repeated every 2–4 days	5.0	>13 mm, rupture	0/59	0.0	0.0	6.1
All	DSG/EE 150/20					1/507	0.2	0.0	1.1
Sullivan ⁵⁰	GSD/EE 60/15 (24/4) GSD/EE 60/15 (21/7)	3	Cycles 1, 2, 3: every 2 days	5.0	>13 mm, rupture	0/30	0.0	0.0	11.6
Rossmann ⁵¹	NET/EE 500/20	3	Cycles 1, 2, 3: every 2 days	5.0	>13 mm, rupture	1/28	3.6	0.9	18.3
Murphy ⁵⁴	NETA/EE 1000/20	2	Cycle 1, 2, 3: Days 6, 7, 8, if activity repeated every 2–4 days	9.6	>13 mm, rupture	0/59	0.0	0.0	6.1
Klipping ⁵⁵	DSP/EE 3000/20 21/7 <i>idem</i> , miss Cycle 3, Days 1–3	2	Cycle 2: twice weekly (US), 7–10-day intervals (P)	5.0	>19 mm	1/16	6.3	0.2	30.2
	DSP/EE 3000/20 24/4 <i>idem</i> , miss Cycle 3, Days 1–3	2	Cycle 2: every 3rd day	5.0	>13 mm, rupture	1/52	1.9	0.1	10.3
	DSP/EE 3000/20 24/4 <i>idem</i> , miss Cycle 3, Days 1–3	2	Cycle 3: every 3rd day	5.0	>13 mm, rupture	4/52	7.7	2.1	18.5
	DSP/EE 3000/20 24/4 <i>idem</i> , miss Cycle 3, Days 1–3	2	Cycle 2: every 3rd day	5.0	>13 mm, rupture	0/52	0.0	0.0	6.8
	DSP/EE 3000/20 24/4 <i>idem</i> , miss Cycle 3, Days 1–3	2	Cycle 3: every 3rd day	5.0	>13 mm, rupture	1/52	1.9	0.0	10.3
All 15-20 µg EE OCS						12/1030	1.1	0.6	2.0

Values resulting from studies with scheduled omissions in tablet intake (in italics) were not included in the calculation of totals. CI, confidence interval; COC, combined oral contraceptive; DSG, desogestrel; DSP, drospirenone; EE, ethinylestradiol; GSD, gestodene; LL, lower limit; LNG, levonorgestrel; NA, not applied for ovulation assessment; ND, not done; NET, norethisterone; NETA, norethisterone acetate; NPD, not predefined; P, progesterone; PFI, pill-free interval; UL, upper limit; US, ultrasound.

Table 3 Ovulation in studies with phasic combined oral contraceptives

Reference	Progestogen/EE µg/µg	Duration (cycles)	Schedule for determination of ovulation	Ovulation criteria		Ovulation occurrence (subjects)	Ovulation rate	
				P (nmol/l)	US		%	95% CI
				P	US		LL	UL
Vange ¹⁸	TriLNG/EE	6	Cycles 1, 3, 6: every 4 days	16.0	Rupture	5/10	18.7	81.3
Landgren ³²	TriLNG/EE (PFI 10 days)	1	Cycle 1: every 2 days	16.0	NA	1/10	0.3	44.5
Westcombe ⁶²	TriLNG/EE	3	Cycles 1, 2, 3: Days 4, 8, 10, 12, 18 or 19	16.0	ND	4/46	8.7	20.8
Does ⁵⁹	TriLNG/EE	6	Cycles 1, 3, 6: Days 3, 7, 10, 14, 17, 21, 23, 28 (US); Days 3, 10, 17, 23, 28 (P)	5.0	>15 mm, rupture	1/15	6.7	32.0
Kuhl ³³	TriLNG/EE	3	Cycle 3: Days 6, 11, 21, 28	9.6	ND	2/11	18.2	51.8
Ende ⁵⁶	TriLNG/EE	2	Cycle 2: Days 14–16, 20–23, 27–1	8.0	ND	0/20	0.0	16.8
Killick ⁵⁷	TriLNG/EE	1	Cycle 1: Days 2, 4, 8, 10, 12, 16, 18, 22, 25, 28	NPD	NPD	0/22	0.0	15.4
Rabe ¹⁷	TriLNG/EE	1	Cycle 1: once between Days 10–12 and Days 16–18	4.5	NA	0/53	0.0	6.7
Prierson ⁴²	TriLNG/EE	3	Cycle 1: every 2 days; Cycle 2: weekly; Cycle 3: every 3 days (US); P once, when indicated by US	9.6	Rupture	4/22	18.2	40.3
All	TriLNG/EE					16/199	8.0	4.7
Vange ¹⁸	TriGSD/EE	6	Cycles 1, 3, 6: every 4 days	16.0	Rupture	0/10	0.0	30.8
Elomaa ²³	TriGSD/EE	2	Cycle 2: Days 1, 2, 3, 5, 7, 26, 28	9.6	NA	0/34	0.0	10.3
Spona ⁸	TriGSD/EE	1	Not indicated	NPD	NPD	0/20	0.0	16.8
Shaw ⁵⁸	TriGSD/EE	6	Cycles 1, 2, 6: Days 2, 4, 8, 12, 16, 18, 22, 25, 28	NPD	NPD	0/25	0.0	13.7
All	TriGSD/EE					0/89	0.0	4.1
Creinin ⁴³	TriNGM/EE 100/20 (PFI 9 days)	2	Cycle 2: Days 10, 14, 21, 28	9.6	NPD	2/37	5.4	18.2
Rabe ¹⁷	TriNGM/EE	1	Cycle 1: once between Days 10–12 and Days 16–18	4.5	NA	0/38	0.0	9.3
Prierson ⁴²	TriNGM/EE	3	Cycle 1: every 2 days; Cycle 2: weekly; Cycle 3: every 3 days (US); P once, when indicated by US	9.6	Rupture	4/25	16.0	36.1
All	TriNGM/EE					4/63	6.3	1.8
Does ⁵⁹	TriDSSG/EE	8	Cycles 1, 3, 6: Days 3, 7, 10, 14, 17, 21, 23, 28 (US); Days 3, 10, 17, 23, 28 (P)	5.0	>15 mm, rupture	0/16	0.0	20.6
Crosignani ⁴⁹	TriDSSG/EE	8	Cycles 3 or 4, 6, 7 or 8: 2 times between Days 7–13 and Days 16–20	NPD	NPD	0/22	0.0	15.4
All	TriDSSG/EE					0/38	0.0	9.3
Letterie ⁶¹	TriNET (miss 4 tablets)	1	Cycle 1: every 4 days	NPD	>13 mm	0/15	0.0	21.8
Grimes ²⁸	TriNET/EE	6	Cycles 1–6: Day 21 (P); Cycles 1, 2, 3, 6: weekly (US)	9.6	NA	1/10	10.0	44.5
Hamilton ⁶³	TriNET/EE	2	Cycle 1: Days 23–28 daily; Cycle 2: Days 1–14 every 2 days, Days 15–28 every 4 days (US)	NPD	Rupture	0/12	0.0	26.5
All	TriNET/EE (miss 1 tablet)					1/18	5.6	27.3
All	TriNET/EE					1/22	4.5	0.1
Vange ¹⁸	BIDSG/EE	6	Cycles 1, 3, 6: every 4 days	16.0	Rupture	0/10	0.0	30.8
Ende ⁵⁶	BIDSG/EE	2	Cycle 2: Days 14–16, 20–23, 27–1	8.0	ND	0/20	0.0	16.8
Kuhl ⁶⁰	BIDSG/EE	6	Cycles 1, 3, 6: Days 18–22	NPD	ND	0/19	0.0	17.6
All	BIDSG/EE					0/49	0.0	7.3
All phasic combined OCS						21/460	4.6	2.8

Values resulting from studies with scheduled omissions in tablet intake (in italics) were not included in the calculation of totals. Bi, biphasic; CI, confidence interval; COC, combined oral contraceptive; CPA, cyproterone acetate; DSG, desogestrel; EE, ethinyloestradiol; GSD, gestodene; LL, lower limit; LNG, levonorgestrel; NA, not applied for ovulation assessment; ND, not done; NET, norethisterone; NGM, norgestimate; NPD, not predefined; P, progesterone; PFI, pill-free interval; Tri, triphasic; UL, upper limit; US, ultrasound.

criterion would have resulted in four ovulations out of 25 (16.0%) subjects. Another study using the same criteria observed no ovulations amongst 24 subjects over three cycles, although one (4.2%) subject had a progesterone level of >16 nmol/l.³⁹ Also, in a study in which the first two tablets of Cycle 2 were omitted, 4/35 (11.4%) subjects ovulated (progesterone >9.6 nmol/l) in that cycle.⁴³ No ovulations were observed in three studies using GSD/EE 75/20 µg and progesterone levels of >5 nmol/l^{45,47} or >9.6 nmol/l.⁴⁴ A COC containing 60 µg GSD and 15 µg EE is also available in a regimen of 24 active pills and 4 pill-free days. In a study using an ovulation definition of serum progesterone >5 nmol/l combined with follicle diameter of >13 mm plus rupture, no ovulations were observed in 30 women treated for three cycles, while one woman out of 28 ovulated using this combination in a 'classical' regimen of 21 active pills and 7 pill-free days.⁵⁰ In the study of Klipping *et al.*⁵⁵, formulations consisting of drospirenone (DSP) 3 mg and EE 20 µg were also investigated in two regimens that differed in the length of the pill-free period. Using the same criteria as the aforementioned study, one woman out of 52 on the 'classical' 21/7 regimen and no one out of 52 on the 24/4 regimen ovulated during Cycle 2. Deliberate omission of the first three pills of the Cycle 3 resulted in four and one woman, respectively, ovulating during Cycle 3 in the 21/7 and 24/4 regimen. Ovulations were not observed in three studies conducted with DSG/EE 150/20 µg and using progesterone levels of >9.6 nmol/l,²³ >5 nmol/l⁴⁷ or >4.9 nmol/l.⁵²

Finally, several studies did not measure progesterone at all and relied solely on ultrasound^{24,26} whilst others did not predefine the progesterone level indicative of ovulation^{46,48,49,52} or did not perform measurements during the critical days for escape ovulation.^{17,40–42,51,54}

Phasic COCs

Table 3 shows the studies performed with triphasic (Tri) or biphasic (Bi) COCs.^{8,17,18,23,28,32,33,42,43,49,56–63} Overall, 21 out of 460 (4.6%) subjects were found to have ovulated. Differences between the various types of COC were observed, with the ovulation incidence ranging from 0.0% to 8.0%. The upper limits of the 95% CIs also varied widely between studies, ranging from 6.7% to 81.3%. The most commonly studied combination was TriLNG/EE (199 subjects in eight studies) with an ovulation incidence of 8.0%.

There were only three studies that used a progesterone level of >16 nmol/l as the criterion for ovulation. In the study by van der Vange *et al.*¹⁸ in which progesterone was determined every 4 days during Cycles 1, 3 and 6, five out of 10 women ovulated on TriLNG/EE (50%); these were all well-documented cases associated with high peak progesterone levels (24.1–47.7 nmol/l) and follicular growth and rupture shown by ultrasound. In the same study, no woman ovulated on TriGSD/EE or BiDSG/EE. Another study assessed the effect of missing two doses of TriLNG/EE and reported one ovulation in 10 women;³² progesterone was measured every 2 days. The third study unfortunately only measured progesterone on Days 4, 8, 10, 12, 18 or 19 and therefore levels during the critical days for escape ovulation were not taken into account.⁶² Of the 46 women studied, four (8.7%) ovulated.

One possible ovulation among 15 (6.7%) women was reported in a study with TriLNG/EE using ultrasound evidence and progesterone levels of >5 nmol/l.⁵⁹ In the same study, none of 16 women given TriDSG/EE ovulated. Other reports include two ovulations (progesterone >9.6 nmol/l) amongst 11 (18.2%) subjects on TriLNG/EE during one monitored cycle.³³ The deliberate omission of the first

two tablets of Cycle 2 resulted in ovulation (progesterone >9.6 nmol/l) in 2/37 (5.4%) subjects using TriNGM/EE.⁴³ Two other studies reported no ovulations with TriGSD/EE (progesterone >9.6 nmol/l)²³ or BiDSG/EE (progesterone >8 nmol/l).⁵⁶

Although all the studies identified used some measure of progesterone, this was not predefined in several cases^{8,49,57,58,60,61,63} or was not determined in the critical days for escape ovulation in others.^{17,28,42}

POPs

In general, higher ovulation rates are observed in studies with POPs (Table 4), although this does not apply to all formulations.^{64–69} It should be borne in mind, however, that the criteria for determining ovulation were not comparably strict in all studies. There were very marked differences between the traditional POPs (ovulation incidence 42.6%) and the DSG POP (ovulation incidence 1.25%).

Traditional POPs

Using a strict ovulation criterion of progesterone >16 nmol/l for at least 5 days, ovulation incidences of 28.6% (10/35 women) and 39.5% (17/43 women) have been reported with the 300 µg NET POP.^{12,62} One study measured progesterone levels seven times during Cycle 3,⁶⁴ whilst the other measured levels daily during one cycle.¹⁴ High rates of ovulation have also been reported for the 30 µg LNG POP, even when the strict criteria of progesterone >30 nmol/l combined with a follicle diameter of >15 mm plus rupture were applied (28.1% of cycles).⁶⁶ Progesterone levels were determined twice weekly during cycles 7 and 12. A less strict criterion of >30 nmol/l progesterone without ultrasound assessment resulted in an ovulation rate of 37.9%. Two further studies relied on ultrasound data only.^{65,67}

DSG POP

In contrast to these findings, consistently low levels of ovulation have been observed with 75 µg DSG daily.

In the previously cited study,⁶⁶ there was one ovulation in 59 cycles (1.7%) of 75 µg DSG, using a strict definition of progesterone >30 nmol/l combined with a follicle diameter of >15 mm plus rupture. Progesterone levels indicative of an absence of luteinisation (<10 nmol/l) were achieved during the first assessed cycle (Cycle 7) in almost all women (97%) given DSG compared with only 34% of those given LNG ($p < 0.001$). The percentages of women with progesterone levels <10 nmol/l during the second assessed cycle (Cycle 12) were 97% and 50%, respectively. This was supported by the incidence of follicular rupture that occurred in 6% and 3% of women in the DSG group at Cycles 7 and 12, respectively, compared with 31% and 36% of the women in the LNG group.

Using an ovulation criterion of progesterone >16 nmol/l plus a follicle diameter of >15 mm plus rupture, Obruca *et al.*⁶⁸ reported no ovulations amongst 13 women using 75 µg DSG. Progesterone levels were measured daily during one cycle. Two further studies, which used the less strict criterion of progesterone >10 nmol/l, reported no ovulations in 14 women¹¹ and 23 women,⁶⁹ respectively.

Considering the narrow timing of the dosing window afforded by most POPs, the effects of a 12-hour delay in tablet intake were investigated with 75 µg DSG.¹³ Of 103 women who received DSG for two cycles and who were scheduled to take their tablets 12 hours late on Days 11, 14 and 21 of either the first or second cycle, only one (1%) woman was found to ovulate according to the strict criterion of progesterone >16 nmol/l for 5 days.

Table 4 Ovulation in studies with progestogen-only pills

Reference	Progestogen µg	Duration (cycles)	Schedule for determination of ovulation	Ovulation criteria		Ovulation occurrence (subjects)	Ovulation rate	
				P (nmol/l)	US		%	95% CI
							LL	UL
Kim-Bjorklund ⁶⁴	NET 300	3	Cycle 3: 7 times	>16, >5 days	NPD	10/35	28.6	14.6
Landgren ¹⁴	NET 300	1	Cycle 1: Days 1–28 daily	>16, >5 days	ND	17/43	39.5	25.0
Chitlange ⁶⁵	NET 300	2	Cycles 1, 2: daily	NPD	Rupture	3/8 ^a	37.5	8.5
All	NET 300					30/86	34.9	24.9
Rice ⁶⁶	LNG 30	12	Cycles 7, 12: 2 times/week	>30	>15 mm, rupture	16/57 ^b	28.1	17.0
				>30	–	11/29	37.9	20.7
				>10	>15 mm, rupture	18/57 ^b	31.6	19.9
				>10	–	19/29	65.5	45.7
Tayob ^{67c}	LNG 30/NET 350/EDA 500	>6	Cycle >6: 3 times/cycle	ND	Rupture	6/21	28.6	11.3
All	LNG 30					19/29	65.5	45.7
All	LNG 30 and NET 300					59/115	42.6	33.4
Rice ⁶⁶	DSG 75	12	Cycles 7, 12: 2 times/week	>30	>15 mm, rupture	1/59 ^b	1.7	0.04
				>30	–	0/30	0.0	0.0
				>10	>15 mm, rupture	2/59 ^b	3.4	0.4
				>10	–	1/30	3.3	0.08
Obruca ⁶⁸	DSG 75	1	Cycle 1: daily	>16	>15 mm, rupture	0/13	0.0	0.0
Rice ⁶⁶	DSG 75	7	Cycles 1, 2, 7: 2 times/week	>10	NPD	0/14	0.0	0.0
Heusden ⁶⁹	DSG 75	7	Cycle 3: every 2 days; or Cycle 4 or 5: 2 times/week	>10	NPD	0/23	0.0	0.0
Korver ¹³	DSG 75 (12-hour delay 3 days)	2	Cycles 1, 2: every 2nd day	>16, >5 days	NPD	1/103	1.0	0.02
All	DSG 75			>10		1/80	1.25	0.03

Values in italics were not included in the calculation of totals. CI, confidence interval; DSG, desogestrel; EDA, ethynodiol acetate; LNG, levonorgestrel; ND, not done; NET, norethisterone; NPD, not predefined; P, progesterone; UL, upper limit; US, ultrasound.

^aThree ovulations are reported in 16 cycles; it has been assumed that the three ovulations occurred in three different subjects.

^bFigures reflect the number of cycles, not the number of subjects.

^cResults not presented per type of pill used; the study was therefore not considered in the total calculation for LNG 30.

Progesterone was measured every second day over two cycles. Return of ovulation took at least 7 days after DSG was stopped, although all women had ovulated within 30 days.

Discussion

The overall incidence of ovulation determined by this literature search was 2.0% with 30–35 µg EE COCs, 1.1% with 15–20 µg EE COCs, 4.6% with phasic COCs, 1.25% with the DSG POP and 42.6% with traditional POPs. Although some of the progestogens used in the 30–35 µg EE COCs appeared to be associated with somewhat higher rates of ovulation (e.g. NET, DSP and CPA), this may have been due to the small number of studies conducted with these formulations. In contrast, the ovulation rate with 15–20 µg EE COCs was notably higher with preparations containing the progestogen LNG; the overall incidence of ovulation was 8.6% (9/105) in a total of five studies. This incidence would have been further increased if the more accurate criterion of progesterone levels >16 nmol/l was applied to the studies for which it was available.^{39,40,42} Ovulation rates with the various types of phasic COCs were also highest with TriLNG/EE, with an incidence of 16/199 (8.0%) in a total of eight studies. However, the greatest difference between the progestogens was observed with the POPs. The highest ovulation rates amongst all the oral contraceptives were seen with 300 µg NET POPs [30/86 (34.9%) subjects in three studies] and 30 µg LNG POPs [19/29 (65.5%) subjects in one study]. The 75 µg DSG POP Cerazette was a notable exception, with just one woman out of 80 (1.3%) ovulating in four studies, which is comparable to COCs.

Adequately timed and frequent sampling of serum for determination of progesterone levels is considered a prerequisite for detecting ovulation. Many of the studies cited in this literature review do not fulfil this criterion. In particular, the largest study,²⁴ which included 207 subjects on DSG/EE 150/20 µg and 209 on GSD/EE 75/30 µg, did not measure progesterone levels. In addition, the frequency and timing of ultrasound scans (four scans during the least critical period for escape ovulation) were insufficient to draw conclusions, as illustrated by the fact that a pregnancy occurred despite the reported absence of ovulation. It should also be noted that interpretation of an ultrasound can be ambiguous. Even in a physiological menstrual cycle, the wide range of pre-ovulatory follicle sizes and the varying ultrasonic appearance of the corpora lutea preclude the use of follicular diameter as the sole criterion for ovulation. The situation is even more complex in women taking steroid contraception due to disturbed folliculogenesis and the presence of multiple follicles.⁷⁰ Serum progesterone levels appear to be a more robust parameter in view of the steep rise observed after ovulation. Regular blood sampling during the menstrual cycle of normally menstruating women revealed that post-ovulatory maximum progesterone levels were considerably greater than 16 nmol/l in all women and that these levels were maintained for at least 5 days in 95% of women.^{14,15} Progesterone levels of >16 nmol/l sustained for at least 5 days would therefore appear to be a good indicator of ovulation. The timing of measurements is also important; with COCs the risk of escape ovulation increases with each day of the routinely scheduled pill-free-interval (usually Days 22–28), reaching its peak during the first few days after tablet intake is resumed.⁷¹ It therefore appears that both frequent and adequately timed sampling of serum progesterone is a prerequisite for detecting ovulation.

Unfortunately, many of the studies that used adequate

criteria for ovulation only included a small number of subjects. Moreover, interpretation of the data is hampered by methodological differences between the studies, in particular the definition of ovulation, the frequency and timing of measurements, the duration of study, and the bioanalytical and statistical methods, as well as by a lack of detail in the publications. In addition, the possibility of selective publication cannot be ruled out.

In general, however, the data show that COCs, as well as the desogestrel POP, are effective in suppressing ovulation, whilst the traditional POP formulations are not as reliable. Nevertheless, the ovulation suppression with COCs is not complete; monophasic COCs containing 15–20 µg EE or 30–35 µg EE show overall incidences of 1.0% and 2.0%, respectively, with phasic COCs appearing a little less effective with an overall incidence of 4.6%. Some formulations within these categories show substantially higher incidences, but whether this reflects a true difference in potency or just a difference in study design is difficult to determine. The findings with traditional POPs in general confirm that these contraceptives do not primarily rely on ovulation inhibition as the mechanism of action, with an overall ovulation incidence of 42.6%. The DSG POP is different in this respect, with an overall ovulation incidence of 1.25%, comparable to that achieved with the COCs.

It is difficult to extrapolate for each formulation the observed differences in ovulation inhibition to actual contraceptive failure rates. From published clinical trial failure data it is often not clear on the basis of which criteria subjects were selected, which (sub-)population was used for the analysis (e.g. evaluable subjects, intent-to-treat or per protocol dataset) and whether subjects not at risk were excluded from the overall exposure. In addition, failure rates may be expressed as 'method', 'user' or overall failure rate, but the criteria applied to make these distinctions are not always clear; besides, failure rates may be differently expressed, either as Pearl indices or as Life Table rates (with either 6-month, 1-year or 2-year rates presented). Variation also exists between studies in the number of subjects studied and the study duration, both of which may significantly impact reported Pearl indices. Also, the level of control exerted during a study may have a major impact on subject compliance and failure, but can often not be deduced from publications. Notwithstanding these limitations, the general trend that emerges from published clinical trial failure rates is consistent with that of the ovulation rates reported here. That is, published failure rates (Pearl indices) range from 0.0 to 1.55 for monophasic OCs containing either 30 µg or 20 µg EE, from 0.25 to 4.4 for triphasic pills and from 0.5 to 13.0 for (traditional) POPs. Surveys from abortion registries constitute another possible source of information on determinants of contraceptive failure. Some surveys have attempted to distinguish between the types of pills used around the time of unintended pregnancy. A survey conducted in The Netherlands⁷² revealed a significantly increased proportion of sequential and phasic pill users among pill failures than in the general population, while also the proportion of traditional POP users among failures was higher than predicted from their market share. In a New Zealand survey,⁷³ it was observed that most COCs failed as expected from their respective market shares, but this time no difference was apparent between monophasic and phasic COCs. Conversely, POP users were over-represented among failures, accounting for 18.4% of failures at a market share of 11.0%.

The traditional POP options available to date are

limited by their reduced efficacy, their requirement for strict adherence to the dosing schedule, and the occurrence of irregular vaginal bleeding; they are therefore generally recommended mainly for older women and those who are breastfeeding.

The potentially greater efficacy of the DSG POP compared with traditional POPs has been confirmed in a large double-blind, randomised, multicentre study.⁷⁴ A total of 1320 healthy women received either the DSG POP ($n = 989$) or LNG 30 µg/day ($n = 331$) for 13 consecutive treatment periods of 28 days. The total exposure was 728 woman-years to the DSG POP and 258 woman-years to LNG. The proportion of women who were starting contraception for the first time (starters), who were switching from another form of contraception (switchers) or who were breastfeeding at the start of the study was similar and was comparable in the two groups. Overall, there were three pregnancies in the DSG POP group and four in the LNG group, resulting in Pearl indices (number of pregnancies per 100 women-years) of 0.41 and 1.55, respectively. Two pregnancies in the DSG POP pill group and one in the LNG group could be attributed to gross non-compliance (tablets deliberately stopped, missed for several days or taken irregularly), resulting in one pregnancy during the DSG POP use and three during LNG use, resulting in 'perfect use' Pearl indices of 0.14 and 1.17, respectively.

Good compliance is essential to maintain contraceptive efficacy. This is somewhat easier to achieve with the DSG POP than with traditional POPs due to its greater flexibility. As the effect of traditional POPs on cervical mucus is maintained for only about 27 hours, the pills must be taken within a strict 3-hour window each day. Because such mucosal changes are less important as a mechanism of contraception with the desogestrel POP, which relies mainly on inhibition of ovulation, a delay in pill intake of up to 12 hours will not affect its efficacy.¹³

In conclusion, although some of the studies are hampered by inadequate ovulation criteria, the literature search indicates that the DSG POP and the (monophasic) COCs share the ability to consistently inhibit ovulation. Thus, the DSG POP pill provides an alternative that is equally effective in preventing ovulation as COCs for women who need to avoid exogenous estrogen exposure.

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