Ovulation incidence with oral contraceptives: a literature review

Ian Milsom, Tjeerd Korver

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.

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 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, etonogestrel9,10 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

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

(Accepted 19 August 2008)

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.

Department of Obstetrics and Gynaecology, Sahlgrenska Academy at Göteborg University, Göteborg, Sweden

Ian Milsom, MD, PhD, Professor

Global Clinical Development, Schering-Plough Research Institute, Oss, The Netherlands

Tjeerd Korver, PhD, Clinical Group Director Gynaecology

Correspondence to: Dr Tjeerd Korver, Global Clinical Development, Schering-Plough Research Institute, PO Box 20, 5340 BH, Oss, The Netherlands. E-mail: tjeerd.korver@spcorp.com
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, 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, 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.

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 RateS) or (OvarS adj ActivS) or (Escap$ adj OvulatS)] 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 fulfill 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) 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.

**Results**

**COCs containing 30–35 µg EE**

Studies employing COCs containing 30–35 µg EE are shown in Table 1. 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 and 10 users of norethisterone (NET)/EE 1000/35 µg. 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 Czecmicky 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. 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.

Amongst the studies that used different progesterone levels to define ovulation, Spona et al. reported no ovulation (progesterone >5 nmol/l) in 22 women using dienogest (DNG)/EE 2000/30 µg, and Elomaa et al. found no ovulation (progesterone >9.6 nmol/l) among 34 women using GSD/EE 75/30 µg. Kuhl et al. reported one ovulation (progesterone >9.6 nmol/l) among 11 subjects using LNG/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. Birch et al. 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) ultrasonic 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, had no predefined definition of ovulation, or did not perform measurements during the most critical days for escape ovulation.

**COCs containing 15–20 µg EE**

Table 2 shows the studies that have been conducted with COCs containing 15–20 µg EE. 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%. LNG/EE 150/20 µg (507 subjects in 10 studies) and GSD/EE (297 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. Application of the progesterone >16 nmol/l
Table 1 Ovulation incidence with oral contraceptives containing 30–35 µg ethinylestradiol

<table>
<thead>
<tr>
<th>Reference</th>
<th>Progestogen/EE µg/µg</th>
<th>Duration (cycles)</th>
<th>Schedule for determination of ovulation</th>
<th>Ovulation criteria</th>
<th>Ovulation occurrence (subjects)</th>
<th>Ovulation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P (nmol/l)</td>
<td>US</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LL</td>
<td>UL</td>
<td></td>
</tr>
<tr>
<td>Vange18</td>
<td>LNG/EE 150/30</td>
<td>6</td>
<td>Cycles 1, 3, 6: every 4 days</td>
<td>16.0</td>
<td>Rupture</td>
<td>0/10</td>
</tr>
<tr>
<td>Landgren20</td>
<td>LNG/EE 150/30 (PFI 9 days)</td>
<td>3</td>
<td>Cycles 1, 2, 3: 3 times/week</td>
<td>16.0</td>
<td>ND</td>
<td>0/10</td>
</tr>
<tr>
<td>Wang42</td>
<td>LNG/EE 150/30 (2 miss)</td>
<td>1</td>
<td>Cycle 1: daily</td>
<td>16.0</td>
<td>ND</td>
<td>0/10</td>
</tr>
<tr>
<td>Kuhl33</td>
<td>LNG/EE 150/30</td>
<td>3</td>
<td>Cycle: Days 6, 11, 21, 28</td>
<td>9.6</td>
<td>ND</td>
<td>2/11</td>
</tr>
<tr>
<td>Schwartz36</td>
<td>NG/EE 300/30 (Day 1 start)</td>
<td>1</td>
<td>Cycle: Days 21, 28</td>
<td>9.6</td>
<td>13 mm (NA)</td>
<td>2/29</td>
</tr>
<tr>
<td></td>
<td>NG/EE 300/30 (Day 4 start)</td>
<td></td>
<td></td>
<td>1.29</td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>NG/EE 300/30 (Day 7 start)</td>
<td></td>
<td></td>
<td>0.27</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Smith19</td>
<td>LNG/EE 150/30 (21 days)</td>
<td>&lt;1</td>
<td>Last 7 days: every 2 days; PFI: every day</td>
<td>NPD</td>
<td>ND</td>
<td>0/6</td>
</tr>
<tr>
<td>Morris22</td>
<td>LNG/EE 150/30 (1 miss)</td>
<td>1</td>
<td>Cycle: daily from day before miss until 7 days after</td>
<td>NPD</td>
<td>ND</td>
<td>0/10</td>
</tr>
<tr>
<td>Duijkers31</td>
<td>LNG/EE 150/30</td>
<td>2</td>
<td>Cycle: every 3rd day from Day 2, except Days 20–24</td>
<td>16.0</td>
<td>ND</td>
<td>0/19</td>
</tr>
<tr>
<td>Birtch37</td>
<td>LNG/EE 150/30</td>
<td>1</td>
<td>Cycle: once between Days 10–12 and Days 16–18</td>
<td>4.5</td>
<td>NA</td>
<td>0.83</td>
</tr>
<tr>
<td>All</td>
<td>LNG/EE 150/30</td>
<td>3</td>
<td>Cycles 1, 2, 3: Days 7, 14, 21, 24, 28; daily if follicle ≥14 mm</td>
<td>NPD</td>
<td>15 mm, CL next day</td>
<td>1.8</td>
</tr>
<tr>
<td>Elomaa23</td>
<td>GSD/EE 75/30</td>
<td>2</td>
<td>Cycle 2: Days 1, 2, 3, 5, 7, 26, 28</td>
<td>9.6</td>
<td>NA</td>
<td>0/3</td>
</tr>
<tr>
<td>Teichmann24</td>
<td>LNG/EE 75/30</td>
<td>9</td>
<td>Cycles 1, 3, 6: daily during Days 18–21 (US)</td>
<td>ND</td>
<td>Rupture</td>
<td>0.29</td>
</tr>
<tr>
<td>Thomas25</td>
<td>GSD/EE 75/30</td>
<td>6</td>
<td>Cycles 1, 3, 6: Days 8–17, Day 21 (P)</td>
<td>4.5</td>
<td>NA</td>
<td>0/18</td>
</tr>
<tr>
<td>Rabe37</td>
<td>GSD/EE 75/30</td>
<td>1</td>
<td>Cycle: once between Days 10–12 and Days 16–18</td>
<td>4.5</td>
<td>NA</td>
<td>0.16</td>
</tr>
<tr>
<td>All</td>
<td>GSD/EE 150/30</td>
<td>1</td>
<td>Cycle: every 3rd day from Day 2, except Days 20–24</td>
<td>4.5</td>
<td>NA</td>
<td>0.277</td>
</tr>
<tr>
<td>Vange18</td>
<td>DSG/EE 150/30</td>
<td>6</td>
<td>Cycles 1, 3, 6: every 4 days</td>
<td>16.0</td>
<td>Rupture</td>
<td>0/10</td>
</tr>
<tr>
<td>Landgren28</td>
<td>DSG/EE 150/30 (PFI 10 days)</td>
<td>1</td>
<td>Cycle 1: every 2 days</td>
<td>16.0</td>
<td>NA</td>
<td>1/10</td>
</tr>
<tr>
<td>Kuhl33</td>
<td>DSG/EE 150/30</td>
<td>3</td>
<td>Cycle 3: Days 6, 11, 21, 28</td>
<td>9.6</td>
<td>ND</td>
<td>1/11</td>
</tr>
<tr>
<td>Heusden36</td>
<td>DSG/EE 150/30</td>
<td>2</td>
<td>Cycle 2: daily during PFI (Days 22–28)</td>
<td>ND</td>
<td>NPD</td>
<td>0/12</td>
</tr>
<tr>
<td>Rabo37</td>
<td>DSG/EE 150/30</td>
<td>1</td>
<td>Cycle: once between Days 10–12 and Days 16–18</td>
<td>4.5</td>
<td>NA</td>
<td>0/19</td>
</tr>
<tr>
<td>All</td>
<td>DSG/EE 150/30</td>
<td>1</td>
<td>Cycle: Days 1, 2, 3, 5, 7, 26, 28</td>
<td>9.6</td>
<td>NA</td>
<td>0/10</td>
</tr>
<tr>
<td>Vange18</td>
<td>NET/EE 1000/35</td>
<td>6</td>
<td>Cycles 1, 3, 6; every 4 days</td>
<td>16.0</td>
<td>Rupture</td>
<td>0/10</td>
</tr>
<tr>
<td>Grimes28</td>
<td>NET/EE 1000/35</td>
<td>6</td>
<td>Cycles 1–6: Day 21 (P); Cycles 1, 2, 3, 6: weekly (US)</td>
<td>9.6</td>
<td>NA</td>
<td>0/10</td>
</tr>
<tr>
<td>Chowdhury34</td>
<td>NETA/EE 1000/30</td>
<td>1</td>
<td>Cycle 1: Days 22–25 daily</td>
<td>12.8</td>
<td>NA</td>
<td>1/10</td>
</tr>
<tr>
<td>All</td>
<td>NET(A)/EE 1000/30</td>
<td>1</td>
<td>Cycles 1, 2, 3; Days 7, 14, 21, 24, 28; daily if follicle ≥14 mm</td>
<td>1.29</td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>Heodon23</td>
<td>NGM/EE 250/35</td>
<td>1</td>
<td>Cycle 1: US every 2 days; P when indicated</td>
<td>NPD</td>
<td>NPD</td>
<td>0/5</td>
</tr>
<tr>
<td>Birtch37</td>
<td>NGM/EE 250/35</td>
<td>1</td>
<td>Cycle 1: once between Days 10–12 and Days 16–18</td>
<td>4.5</td>
<td>NA</td>
<td>0/3</td>
</tr>
<tr>
<td>All</td>
<td>NGM/EE 250/35</td>
<td>1</td>
<td>Cycle 1: US every 2 days; P when indicated</td>
<td>NPD</td>
<td>NPD</td>
<td>1/8</td>
</tr>
<tr>
<td>Vange18</td>
<td>CPA/EE 2000/35</td>
<td>6</td>
<td>Cycles 1, 3, 6; every 4 days</td>
<td>16.0</td>
<td>Rupture</td>
<td>1/10</td>
</tr>
<tr>
<td>Spaona30</td>
<td>DNG/EE 2000/30</td>
<td>3</td>
<td>Cycles 1, 2, 3; every 2 days</td>
<td>5.0</td>
<td>Rupture</td>
<td>0/22</td>
</tr>
<tr>
<td>Grimes28</td>
<td>NET/EE 500/35</td>
<td>6</td>
<td>Cycles 1–6: Day 21 (P); Cycles 1, 2, 3, 6: weekly (US)</td>
<td>9.6</td>
<td>NA</td>
<td>3/10</td>
</tr>
<tr>
<td>Rosenbaum35</td>
<td>DSP/EE 2000/30</td>
<td>3</td>
<td>Cycles 1, 2, 3: Days 4–20 daily</td>
<td>5.0</td>
<td>Rupture</td>
<td>3/23</td>
</tr>
<tr>
<td>All</td>
<td>30–35 µg EE OCs</td>
<td></td>
<td></td>
<td>1/46</td>
<td>2.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Reference</th>
<th>Progestogen/EE µg</th>
<th>Duration Schedule for determination of ovulation</th>
<th>Ovulation criteria</th>
<th>Ovulation occurrence (subjects)</th>
<th>US</th>
<th>% 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coney38</td>
<td>LNG/EE 100/20</td>
<td>Cycles 1, 2, 3: 3 times/week</td>
<td>&gt;13 mm, rupture</td>
<td>2/25</td>
<td>8.0</td>
<td>1.0 26.0</td>
</tr>
<tr>
<td>Spona39</td>
<td>LNG/EE 100/20</td>
<td>Cycles 1, 2, 3: every 2 days</td>
<td>&gt;13 mm, rupture</td>
<td>0/24</td>
<td>0.0</td>
<td>0.0 14.2</td>
</tr>
<tr>
<td>Creinin43</td>
<td>LNG/EE 100/20 (PFI 9 days)</td>
<td>Cycles 1: Days 10, 14, 21, 28</td>
<td>9.6</td>
<td>4/35</td>
<td>11.4 0.8 23.2</td>
<td></td>
</tr>
<tr>
<td>Koch40</td>
<td>LNG/EE 100/20</td>
<td>Cycles 1, 2, 3: Days 1, 7, 14, 20</td>
<td>&gt;13 mm, rupture</td>
<td>0/18</td>
<td>0.0</td>
<td>0.0 18.5</td>
</tr>
<tr>
<td>Pierson42</td>
<td>LNG/EE 100/20</td>
<td>Cycles 1: every 2 days; Cycle 2: weekly; Cycle 3: every 3 days (US); P, once, when indicated by US</td>
<td>&gt;13 mm, rupture</td>
<td>5/25</td>
<td>20.0</td>
<td>4.7 41.4</td>
</tr>
<tr>
<td>Spona45</td>
<td>GSD/EE 75/20 (21/7)</td>
<td>Cycles 1, 2, 3: every 2 days</td>
<td>&gt;13 mm, rupture</td>
<td>0/30</td>
<td>0.0</td>
<td>0.0 11.6</td>
</tr>
<tr>
<td>Fitzgerald47</td>
<td>GSD/EE 75/20</td>
<td>Days 2, 4, 8, 10; Days 11–18</td>
<td>Rupture</td>
<td>0/19</td>
<td>0.0</td>
<td>0.0 17.6</td>
</tr>
<tr>
<td>Elomaa23</td>
<td>DSG/EE 150/20</td>
<td>Cycle 2: Days 11 or 12 (US) and 23 (P)</td>
<td>&gt;12 mm, &lt;24 hours</td>
<td>0/31</td>
<td>0.0</td>
<td>0.0 11.2</td>
</tr>
<tr>
<td>Rossmanith51</td>
<td>NET/EE 500/20</td>
<td>Cycle 1, 2, 3: Days 6, 7, 8, if activity repeated every 2–4 days</td>
<td>&gt;13 mm, rupture</td>
<td>0/31</td>
<td>0.0</td>
<td>0.0 11.2</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Reference</th>
<th>Progestogen/EE µµg/µµg</th>
<th>Duration (cycles)</th>
<th>Schedule for determination of ovulation</th>
<th>Ovulation criteria</th>
<th>Ovulation occurrence (subjects)</th>
<th>Ovulation rate %</th>
<th>95% CI (LL, UL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vange18</td>
<td>TriLNG/EE</td>
<td>6</td>
<td>Cycles 1, 3, 6: every 4 days</td>
<td>16.0</td>
<td>Rupture</td>
<td>5/10</td>
<td>50.0 (18.7, 81.3)</td>
</tr>
<tr>
<td>Landgren32</td>
<td>TriLNG/EE (PFI 10 days)</td>
<td>1</td>
<td>Cycle 1: every 2 days</td>
<td>16.0</td>
<td>NA</td>
<td>1/10</td>
<td>10.0 (0.3, 44.5)</td>
</tr>
<tr>
<td>Westcombe62</td>
<td>TriLNG/EE</td>
<td>3</td>
<td>Cycles 1, 2, 3: Days 4, 8, 10, 12, 18 or 19</td>
<td>16.0</td>
<td>ND</td>
<td>4/46</td>
<td>8.7 (2.4, 20.8)</td>
</tr>
<tr>
<td>Does59</td>
<td>TriLNG/EE</td>
<td>6</td>
<td>Cycles 1, 3, 6; Days 3, 7, 10, 14, 17, 21, 23, 28 (US); Days 3, 10, 17, 23, 28 (P)</td>
<td>5.0</td>
<td>&gt;15 mm, rupture</td>
<td>1/15</td>
<td>6.7 (0.2, 32.0)</td>
</tr>
<tr>
<td>Kuhl33</td>
<td>TriLNG/EE</td>
<td>6</td>
<td>Cycles 3: Days 6, 11, 21, 28</td>
<td>9.6</td>
<td>ND</td>
<td>2/11</td>
<td>18.2 (2.3, 51.8)</td>
</tr>
<tr>
<td>Ence56</td>
<td>TriLNG/EE</td>
<td>2</td>
<td>Cycle 2: Days 14–16, 20–23, 27–1</td>
<td>8.0</td>
<td>ND</td>
<td>0/20</td>
<td>0.0 (0.0, 16.8)</td>
</tr>
<tr>
<td>Killick57</td>
<td>TriLNG/EE</td>
<td>1</td>
<td>Cycle 1: Days 2, 4, 8, 10, 12, 16, 18, 22, 25, 28</td>
<td>ND</td>
<td>NPD</td>
<td>0/22</td>
<td>0.0 (0.0, 15.4)</td>
</tr>
<tr>
<td>Rabe17</td>
<td>TriLNG/EE</td>
<td>1</td>
<td>Cycle 1: once between Days 10–12 and Days 16–18</td>
<td>4.5</td>
<td>NA</td>
<td>0/53</td>
<td>0.0 (0.0, 6.7)</td>
</tr>
<tr>
<td>Pierson42</td>
<td>TriLNG/EE</td>
<td>3</td>
<td>Cycle 1: every 2 days; Cycle 2: weekly; Cycle 3: every 3 days (US); P once, when indicated by US</td>
<td>9.6</td>
<td>Rupture</td>
<td>4/22</td>
<td>18.2 (5.2, 40.3)</td>
</tr>
<tr>
<td>All</td>
<td>TriLNG/EE</td>
<td>16/199</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vange18</td>
<td>TriGSD/EE</td>
<td>6</td>
<td>Cycles 1, 3, 6: every 4 days</td>
<td>16.0</td>
<td>Rupture</td>
<td>0/10</td>
<td>0.0 (0.0, 30.8)</td>
</tr>
<tr>
<td>Eloma23</td>
<td>TriGSD/EE</td>
<td>2</td>
<td>Cycle 2: Days 1, 2, 3, 5, 7, 26, 28</td>
<td>9.6</td>
<td>NA</td>
<td>0/34</td>
<td>0.0 (0.0, 10.3)</td>
</tr>
<tr>
<td>Spona43</td>
<td>TriGSD/EE</td>
<td>1</td>
<td>Not indicated</td>
<td>NPD</td>
<td>NPD</td>
<td>0/20</td>
<td>0.0 (0.0, 16.8)</td>
</tr>
<tr>
<td>Shaw58</td>
<td>TriGSD/EE</td>
<td>6</td>
<td>Cycles 2, 6, 12, 18, 16, 22, 25, 28</td>
<td>NPD</td>
<td>NPD</td>
<td>0/25</td>
<td>0.0 (0.0, 13.7)</td>
</tr>
<tr>
<td>All</td>
<td>TriGSD/EE</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creinin43</td>
<td>TriNGM/EE 100/20 (PFI 9 days)</td>
<td>2</td>
<td>Cycle 2: Days 10, 14, 21, 28</td>
<td>9.6</td>
<td>NPD</td>
<td>2/37</td>
<td>5.4 (1.7, 18.2)</td>
</tr>
<tr>
<td>Rabe17</td>
<td>TriNGM/EE</td>
<td>1</td>
<td>Cycle 1: once between Days 10–12 and Days 16–18</td>
<td>4.5</td>
<td>NA</td>
<td>0/38</td>
<td>0.0 (0.0, 9.3)</td>
</tr>
<tr>
<td>Pierson42</td>
<td>TriNGM/EE</td>
<td>3</td>
<td>Cycle 1: every 2 days; Cycle 2: weekly; Cycle 3: every 3 days (US); P once, when indicated by US</td>
<td>9.6</td>
<td>Rupture</td>
<td>4/25</td>
<td>16.0 (4.5, 36.1)</td>
</tr>
<tr>
<td>All</td>
<td>TriNGM/EE</td>
<td>4.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does59</td>
<td>TriDSG/EE</td>
<td>6</td>
<td>Cycles 1, 3, 6; Days 3, 7, 10, 14, 17, 21, 23, 28 (US); Days 3, 10, 17, 23, 28 (P)</td>
<td>5.0</td>
<td>&gt;15 mm, rupture</td>
<td>0/16</td>
<td>0.0 (0.0, 20.6)</td>
</tr>
<tr>
<td>Crosignan49</td>
<td>TriDSG/EE</td>
<td>8</td>
<td>Cycles 3 or 4, 6, 7 or 8 or 2 times between Days 7–13 and Days 16–20</td>
<td>NPD</td>
<td>NPD</td>
<td>0/22</td>
<td>0.0 (0.0, 15.4)</td>
</tr>
<tr>
<td>All</td>
<td>TriDSG/EE</td>
<td>0.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lettner61</td>
<td>TriNET (miss 4 tablets)</td>
<td>1</td>
<td>Cycle 1: every 4 days</td>
<td>NPD</td>
<td>&gt;13 mm</td>
<td>0/15</td>
<td>0.0 (0.0, 21.8)</td>
</tr>
<tr>
<td>Grimes28</td>
<td>TriNET/EE</td>
<td>6</td>
<td>Cycles 1–6: Day 21 (P); Cycles 1, 2, 3, 6: weekly (US)</td>
<td>9.6</td>
<td>NA</td>
<td>1/10</td>
<td>10.0 (0.3, 44.5)</td>
</tr>
<tr>
<td>Hamilton63</td>
<td>TriNET/EE</td>
<td>2</td>
<td>Cycle 1: Days 23–28 daily; Cycle 2: Days 1–14 every 2 days, Days 15–28 every 4 days (US)</td>
<td>NPD</td>
<td>Rupture</td>
<td>0/12</td>
<td>0.0 (0.0, 26.5)</td>
</tr>
<tr>
<td>All</td>
<td>TriNET/EE</td>
<td>1/18</td>
<td>Cycle 2, Day 18 (P)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vange18</td>
<td>BiDSG/EE</td>
<td>6</td>
<td>Cycles 1, 3, 6: every 4 days</td>
<td>16.0</td>
<td>Rupture</td>
<td>0/10</td>
<td>0.0 (0.0, 30.8)</td>
</tr>
<tr>
<td>Endo56</td>
<td>BiDSG/EE</td>
<td>2</td>
<td>Cycle 2: Days 14–16, 20–23, 27–1</td>
<td>8.0</td>
<td>ND</td>
<td>0/20</td>
<td>0.0 (0.0, 16.8)</td>
</tr>
<tr>
<td>Kuhl50</td>
<td>BiDSG/EE</td>
<td>6</td>
<td>Cycles 1, 3, 6: Days 18–22</td>
<td>NPD</td>
<td>NPD</td>
<td>0/19</td>
<td>0.0 (0.0, 17.6)</td>
</tr>
<tr>
<td>All</td>
<td>BiDSG/EE</td>
<td>0.49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All phasic combined OCs</td>
<td></td>
<td>21/460</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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, ethinylestradiol; 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.
Phasic COCs

Table 3 shows the studies performed with triphasic (Tri) or biphasic (Bi) COCs. 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 (199/20 µg DSG and 15 µg EE) during Cycle 3 in the 21/7 and 24/4 regimen. Ovulations were observed in three studies conducted with DSG/EE 150/20 µg and using progesterone levels of >9.6 nmol/l, >5 nmol/l or >4.9 nmol/l.

Finally, several studies did not measure progesterone at all and relied solely on ultrasound, whilst others did not predefine the progesterone level indicative of ovulation. Alternatively, some studies did not perform measurements during the critical days for escape ovulation.

DSG POP

In contrast to these findings, consistently low levels of ovulation have been observed with 75 µg DSG daily in all the previously cited studies. 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. Progestrone 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 to 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 to 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. 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 women and 23 women, 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. 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Progestogen µg</th>
<th>Duration (cycles)</th>
<th>Schedule for determination of ovulation</th>
<th>Ovulation criteria</th>
<th>Ovulation occurrence (subjects)</th>
<th>Ovulation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim-Bjorklund64</td>
<td>NET 300</td>
<td>3</td>
<td>Cycle 3; 7 times</td>
<td>&gt;16, &gt;5 days</td>
<td>NPD</td>
<td>10/35</td>
</tr>
<tr>
<td>Landgren14</td>
<td>NET 300</td>
<td>1</td>
<td>Cycle 1; Days 1–28 daily</td>
<td>&gt;16, &gt;5 days</td>
<td>ND</td>
<td>17/43</td>
</tr>
<tr>
<td>Chitlange65</td>
<td>NET 300</td>
<td>2</td>
<td>Cycles 1, 2; daily</td>
<td>&gt;16, &gt;5 days</td>
<td>NPD</td>
<td>3/8a</td>
</tr>
<tr>
<td>All</td>
<td>NET 300</td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>30/86</td>
</tr>
<tr>
<td>Rice66</td>
<td>LNG 30</td>
<td>12</td>
<td>Cycles 7, 12; 2 times/week</td>
<td>&gt;30</td>
<td>&gt;15 mm, rupture</td>
<td>16/57b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;30</td>
<td>11/29</td>
</tr>
<tr>
<td>Tayob67c</td>
<td>LNG 30/NET 350/EDA 500</td>
<td>&gt;6</td>
<td>Cycle &gt;6; 3 times/cycle</td>
<td></td>
<td>ND</td>
<td>19/29</td>
</tr>
<tr>
<td>All</td>
<td>LNG 30</td>
<td></td>
<td></td>
<td></td>
<td>NPD</td>
<td>19/29</td>
</tr>
<tr>
<td>All</td>
<td>LNG 30 and NET 300</td>
<td></td>
<td></td>
<td></td>
<td>NPD</td>
<td>59/115</td>
</tr>
<tr>
<td>Rice66</td>
<td>DSG 75</td>
<td>12</td>
<td>Cycles 7, 12; 2 times/week</td>
<td>&gt;30</td>
<td>&gt;15 mm, rupture</td>
<td>1/59b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;30</td>
<td>0/30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;10</td>
<td>2/59b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;10</td>
<td>1/50</td>
</tr>
<tr>
<td>Obruca68</td>
<td>DSG 75</td>
<td>1</td>
<td>Cycle 1; daily</td>
<td>&gt;16</td>
<td>&gt;15 mm, rupture</td>
<td>0/13</td>
</tr>
<tr>
<td>Rice66</td>
<td>DSG 75</td>
<td>7</td>
<td>Cycles 1, 2, 7; 2 times/week</td>
<td>&gt;10</td>
<td>NPD</td>
<td>0/14</td>
</tr>
<tr>
<td>Heusden69</td>
<td>DSG 75</td>
<td>7</td>
<td>Cycle 3; every 2 days; or Cycle 4 or 5; 2 times/week</td>
<td>&gt;10</td>
<td>NPD</td>
<td>0/23</td>
</tr>
<tr>
<td>Konver13</td>
<td>DSG 75 (12-hour delay 3 days)</td>
<td>2</td>
<td>Cycles 1, 2; every 2nd day</td>
<td>&gt;16, &gt;5 days</td>
<td>NPD</td>
<td>1/103</td>
</tr>
<tr>
<td>All</td>
<td>DSG 75</td>
<td></td>
<td></td>
<td></td>
<td>NPD</td>
<td>1.80</td>
</tr>
</tbody>
</table>

Values in italics were not included in the calculation of totals. CI, confidence interval; DSG, desogestrel; EDA, ethynodiol acetate; LL, lower limit; 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.29,30,42 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 fulfill 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-ovulation serum level 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 failures. From published clinical trial 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 from New Zealand74 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. 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.

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.

Statements on funding and competing interests

Funding Ian Milsom has received research funding from Organon.

Competing interests Tjeerd Korver is an employee of Schering-Plough (formerly Organon), manufacturer of contraceptives including Cerazette.

References


32 Landgren BM, Csemiczky G. The effect on follicular growth and luteal function of "missing the pill": A comparison between a monophasic and a triphasic combined oral contraceptive. *Contraception* 1991; 43: 149–159.


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


