A pre-coital pill? A preliminary in vitro study

Gabor T Kovacs, MD, FRCOG, FRACOG, CREI, Reproductive Gynaecologist, Jacqui Hendricks, BSc Hons, Research Student, Deborah Summerbell, SRN, SRM, Nurse Practitioner; H W Gordon Baker, MD, PhD, FRACP, Andrologist
Monash Medical School, Box Hill Hospital, Victoria, Australia

Correspondence: Professor Gabor T Kovacs, Monash Medical School, Box Hill Hospital, Nelson Road, Victoria 3128, Australia

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Summary
The use of the progestogen-only pill as a ‘pre-coital contraceptive’ was tested by in vitro studies of sperm-mucus interaction. The results suggest that a single tablet of levonorgestrel 30 µg, or norethisterone 350 µg, was effective in preventing sperm migration in the cervical mucus about 12 hours later. This suggests that the progestogen-only pill may be effective as a ‘morning before pill’.

Key words
emergency contraception, mini-pill, progestogen-only contraception

Key message points
• The progestogen-only pill has its maximum effect 10-18 hours after ingestion.
• Conventional advice is that the mini-pill is not effective for 14 days.
• This report suggests that the mini-pill taken orally will make the cervical mucus impenetrable to sperm within 12 hours.
• Women with excessive adipose tissue may find the progestogen-only pill less effective.

Introduction
The contraceptive action of the progestogen-only pill (POP) is multifocal on the endometrium, tubes and ovulation inhibition, but its main action is on the cervical mucus.1 Maximal inhibition of sperm penetration occurs 10-18 hours after ingestion.2 Yet the patient information insert states: ‘It is advisable to use another method of contraception for the first 14 days’. As these two statements are confusing, we decided to investigate the hypothesis that the POP could be used as a ‘morning before pill’. We needed to ascertain whether a single dose of norethisterone 350 µg (Noriday, Syntex, USA), or levonorgestrel 30 µg (Microlut, Schering AG, Berlin) would render the cervical mucus impermeable by spermatozoa 12 hours later.

Method
Subjects were women with azoospermic husbands who were on the waiting list for donor insemination at the Reproductive Medicine Clinic, Prince Henry’s Institute of Medical Research, Melbourne.

The approximate day of ovulation was estimated from previous temperature charts and mucus was evaluated during the oestrogenic pre-ovulatory stage. Women were asked to attend 2-3 days prior to estimated ovulation, and a sample of cervical mucus was obtained using a mucus sampling syringe (Rocket of London). The quantity and quality of mucus was scored according to a modified Insler scale as Cervical Mucus Evaluation Score (CMES).4 This was modified from Insler with a 0-3 point rating for each of the four parameters: mucus volume, fermen, spinnbarkeit and cervical opening, resulting in a score out of 12. Only women who had adequate quantity and quality of mucus were included in the study.

A capillary tube sperm mucus penetration test was then performed5 using fertile donor semen. The distance the sperm had penetrated into the mucus column was examined with a microscope (x 400 magnification) and recorded to the nearest 1 cm (0 to 5 cm). At half the penetration distance the motility of spermatozoa was assessed on up to 100 spermatozoa.

A blood sample was also taken at this time and levels of oestradiol (E2), luteinizing hormone (LH) and progesterone (P2) were assayed.

The women were then asked to take one tablet of the POP, either norethisterone or levonorgestrel, randomly allocated that evening. They returned the following morning 10-12 hours later for mucus evaluation, and the mucus penetration test and hormone assays were repeated. If there was a rise in P2 or LH levels suggesting ovulation and possible physiological change in the mucus, the woman was to be excluded from the study. This did not occur, and no woman was excluded on the basis of spontaneous ovulation.

The change in mucus penetration was analysed by Wilcoxon test for CMES, distance penetrated, and percent progressively motile sperm, and the effect of the two types of progestogen were also compared by Wilcoxon Test.

The study was approved by the Human Research and Ethics Committee of Monash Medical Centre.

Results
Sixteen women were evaluated, eight with levonorgestrel and eight with norethisterone (Table 1). There was no significant difference between the results of the two progestogen preparations (p > 0.05). Four patients had complete inhibition of sperm-mucus penetration with no sperm entering the mucus column. The others had marked reductions in progressive motility. Mucus pH was reduced in some patients.

Three women had no significant change in mucus penetration, two with levonorgestrel and one with norethisterone. These women were extremely obese, all weighing in excess of 75 Kg with Body Mass Index (BMI) greater than 35.

The changes with the two different types of progestogen were then combined and the changes are summarised in Table 2.

None of the women reported any mid-cycle bleeding, nor disruption of the next menstrual period.

Discussion
This preliminary study shows that both the quality of cervical mucus (CMES) (p < 0.001) and sperm penetrability (penetration distance p = 0.001, motility < 0.001) was highly significantly reduced 12 hours after the ingestion of a single tablet of POP (levonorgestrel and norethisterone being equally effective). The pH was reduced, but not
It has to be highlighted that three women who were severely obese with body weight more than 75 Kg and BMI greater than 35 did not respond, and this can probably be explained by the abnormal metabolism/absorption of steroid hormones by adipose tissue. It has previously been suggested that obese women may need larger than the usual dosage of progestogen-only oral contraceptives for efficacy.

Although this method obviously will not be suitable for many couples, there may be situations when intercourse is infrequent and can be anticipated, such as where couples only cohabit on weekends. This concept has been used by the Chinese ‘vacation’ or ‘home visiting’ pills, where couples partake in active sexual activity when they visit each other for short periods.2

**Conclusion**

We recommend that further in vitro and possibly in vivo studies be carried out to assess the efficacy of such a pre-coital pill. Such a method of contraception would add to the options for couples where the woman did not wish to take hormones on a continuous daily basis.

**Acknowledgments**

We wish to thank our patients who took part in the study for their contribution.

**References**


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**Table 1** Results (mean ± standard deviation and range in brackets) of cervical mucus tests before and following treatment with levonorgestrel or norethisterone. There were eight women in each group. There were no significant differences in the results for the two drugs.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Levonorgestrel</th>
<th>Norethisterone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treatment</td>
</tr>
<tr>
<td>CMES (Cervical Mucus Evaluation Score)</td>
<td>10.6 ± 1.5</td>
<td>8.2 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>(8 – 12)</td>
<td>(6 – 12)</td>
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<tr>
<td>Penetration distance (cm)</td>
<td>4.6 ± 1.1</td>
<td>3.2 ± 2.2</td>
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<tr>
<td></td>
<td>(2 – 5)</td>
<td>(0 – 5)</td>
</tr>
<tr>
<td>Progressive motility (%)</td>
<td>72 ± 21</td>
<td>24 ± 33</td>
</tr>
<tr>
<td></td>
<td>(22 – 85)</td>
<td>(0 – 79)</td>
</tr>
<tr>
<td>pH</td>
<td>7.4 ± 0.4</td>
<td>7.3 ± 0.4</td>
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<tr>
<td></td>
<td>(6.4 – 7.7)</td>
<td>(6.3 – 7.7)</td>
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</table>

**Table 2** Changes in cervical mucus and sperm penetration combined for the two different types of POP

<table>
<thead>
<tr>
<th>Mean difference</th>
<th>Range</th>
<th>Wilcoxon test (p)</th>
</tr>
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<tbody>
<tr>
<td>CMES (Cervical Mucus Evaluation Score)</td>
<td>-2.9</td>
<td>-5-0</td>
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<tr>
<td>Penetration distance (cm)</td>
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<td>-5-0</td>
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<tr>
<td>Progressive motility (%)</td>
<td>-53</td>
<td>-89-0</td>
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<tr>
<td>pH</td>
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<td>-1.1-0.5</td>
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