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Comparative study of the effects of a progestogen-only pill containing desogestrel and an intrauterine contraceptive device in lactating women

Ragnheidur I. Bjarnadóttir[a,*], Helga Gottfredsdóttir[a], Kristín Sigurdardóttir, Reynir T. Geirsson[a], Thom O. M. Dieben[b]

Objective To evaluate the effects of desogestrel 75μg/day, as a progestogen-only pill compared with a copper-bearing intrauterine contraceptive device (IUCD) on lactation and to study the safety of both treatments in mothers and children. Transfer of etonogestrel to breast milk was studied in a subgroup of desogestrel users. The children were to be followed up until 2.5 years of age.

Design An open, non-randomised, group-comparative study in lactating women.

Setting University Hospital, Reykjavik, Iceland.

Participants A total of 83 lactating women; 42 received desogestrel and 41 had an IUCD inserted for seven consecutive treatment cycles of 28 days.

Methods Evaluation visits were planned at baseline and at the end of treatment cycles 1, 4 and 7. The amount of breast milk was determined by weighing the infants before and after feeding, at baseline and after treatment cycles 1 and 4. Milk samples were obtained at the same time for constituent measurements. Safety was studied by structured medical examinations and by recording adverse experiences in mothers and children.

Results There were no significant differences between the desogestrel and IUCD groups in composition and quantity of breast milk nor in growth and development of the children followed up to the age of 2.5 years. In the desogestrel group a slightly higher incidence of mild adverse experiences of a hormonal nature was reported among both mothers and infants. Of the children 82% were followed until 1.5 years of age and 50% until 2.5 years.

Conclusion The use of desogestrel 75μg/day did not change the amount and composition of breast milk nor did it affect growth and development of the breastfed children. It appears to be a safe and effective contraceptive method for lactating women

INTRODUCTION

Combined oral contraceptives are not a first choice for breastfeeding women as the oestrogen component may reduce the quantity and adversely change the composition of breast milk. An alternative form of oral hormonal contraception for this group of women is the progestogen-only pill, since by this method breast milk quality and quantity do not appear to change[1,2]. The progestogen-only pills are well tolerated and have a low incidence of side effects. In non-lactating women the main drawbacks of the traditional progestogen-only pill, compared with combined oral contraceptives, are a higher incidence of menstrual irregularities or breakthrough bleeding and lower contraceptive efficacy[3]. Complete inhibition of ovulation is seen in approximately 40% to 50% of cycles with considerable inter-individual variation for conventional progestogen-only pills[3,4]. Contraceptive efficacy depends primarily on the relatively short-lasting effects on the cervical mucus and requires much stricter adherence to the schedule of tablet intake[5]. When women are fully breastfeeding and amenorrhoeic, ovulation will be unlikely to occur and if a progestogen-only pill is added the chances of conceiving will be negligible[6]. With partial breastfeeding, as the contraceptive and bleeding-controlling effects of lactation diminish and cease, the drawbacks of traditional progestogen-only pills may appear and a more effective contraceptive be needed.

The newly introduced desogestrel-containing progestogen-only pill differs from the traditional progestogen-only pills in having a higher contraceptive efficacy. At a daily dose of 75μg desogestrel has been shown outside of lactation to consistently inhibit ovulation[7,8]. A large multicentre efficacy study demonstrated that in all study groups the contraceptive reliability of the desogestrel progestogen-only pill is comparable to the one reported for combined oral contraceptives[9]. However, in order to

[a]*Department of Obstetrics and Gynaecology, University Hospital, Reykjavik, Iceland*
[b]*Clinical Development Department, NV Organon, Oss, The Netherlands*

* **Correspondence**: Dr R. I. Bjarnadóttir, Department of Obstetrics and Gynaecology, University Hospital, 101 Reykjavik, Iceland.

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be a good contraceptive alternative for breastfeeding women, it should be shown that the desogestrel progestogen-only pill does not influence the quantity and quality of breast milk. In this study we have compared the effects of desogestrel 75μg/day and an intrauterine contraceptive device (IUCD) on volume and composition of breast milk and on treatment acceptability. In a subset of the study group we determined the levels of etonogestrel (3-ketodesogestrel, the active metabolite of desogestrel) in breast milk and compared these to the levels in maternal serum. In addition, the effects on infant growth and well-being were assessed after treatment until the age of 2.5 years.

METHODS

In this single-centre, open, non-randomised, group-comparative study a total of 83 women participated. Women were allowed to choose their preferred treatment. They were divided into two groups: 42 received 75μg/day desogestrel (Cerazette, NV Organon, Oss, The Netherlands), while 41 had a Multiload Cu375 intrauterine device fitted (NV Organon, Oss, The Netherlands). Treatment was started at least 28 but not more than 56 days postpartum. Duration of treatment was seven continuous 28-day cycles. Information about the growth and well-being of the breastfed children up to the age of 2.5 years was obtained. A subset of 10 women out of the desogestrel group also participated in a pharmacokinetic study to determine etonogestrel (3-ketodesogestrel) levels in breast milk and blood serum.

All women were healthy volunteers between 18 and 40 years of age, without contraindications to the use of progestogen-only pills (desogestrel group) or IUCDs (IUCD group). Inclusion criteria were full breastfeeding (number of supplementary feedings with formula or animal milk no more than twice a week) and having breastfed after a previous pregnancy for at least three cycles. A pre-pregnancy body weight between 80%–130% of the ideal body weight (according to Metropolitan Life Insurance Company tables) was required. All had given birth to a healthy baby at a gestational age of 259–294 days with a birthweight between the 10^{th} and 90^{th} centile on a nomogram for newborn Icelandic babies[10]. The women had to be ready to continue breastfeeding during the entire seven-cycle study period, to accurately fill in the diary card and patient forms, and to return to the clinic for sample taking. Before starting treatment all women gave written informed consent.

Before treatment all women underwent a general medical and gynaecological examination. A pregnancy test was done to exclude pregnancy. Cervical cytology was obtained if a satisfactory smear test report within the last two years was not available. Haematology, blood chemistry (including liver function tests) and urinalysis were done following the standard procedures of the study centre.

At baseline and at the end of treatment cycle 1 (± 1 week), 4 (± 2 weeks) and 7 (± 2 weeks) maternal weight and blood pressure were recorded and the babies' height, weight, biparietal head circumference and general health evaluated. Diary cards with information on vaginal bleeding patterns and tablet intake were checked and collected, and the women asked about their own well-being and concomitant use of medication, as well as their baby's wellbeing and feeding practices.

Determination of breast milk volume and quality occurred at baseline and around the end of treatment cycles 1 and 4. Breast milk volume was measured by weighing the infant before and after each feeding for 24 hours. The women were given electronic weighing scales (Tanita, Japan) calibrated to an accuracy of ± 5g. Sampling for analysis of milk composition took place in the hospital. The mother breastfed her baby in the hospital, having not fed for at least three hours previously. The other breast was emptied using a breast pump (Medalal, Switzerland). A representative 10mL sample was obtained and deep frozen at -20°C. The amounts of triglycerides, protein and lactose in the milk samples were analysed at the Analytisch Biochemisch Labouratorium (ABL, Assen, The Netherlands).

At each visit after treatment cycles 1, 4 and 7 any adverse experiences were noted. After seven treatment cycles tablet intake was stopped and the women were offered another form of contraception. Those wishing to continue with their IUCD could do so. Information collected routinely during follow up of the children at health centres was obtained where possible to assess child health at the ages of 1.5 and 2.5 years.

In a subset of 10 women in the pill group, the transfer of etonogestrel in breast milk was assessed after treatment cycles 1 and 4. They were hospitalised with their babies from 8.00pm for up to 16 hours after pill intake. Blood samples were taken just before pill intake and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 hours thereafter. A 10mL breast milk sample was taken during every feeding until discharge. An additional 10mL sample was taken from the mid-morning feeding for analysis of milk composition. Serum and milk levels of etonogestrel were determined by radio-immunoassay. Pharmacokinetic parameters were calculated, including the peak concentration of etonogestrel in serum ($C_{max,s}$) and its time of occurrence ($t_{max,s}$); the area under the serum level *versus* time curve from 0 to 24 hours after dosing ($AUC_{0\text{-}24,s}$); the average serum concentration over a 24-hour period ($C_{av,s}$); the peak concentration of etonogestrel in milk ($C_{max,m}$) and its time of occurrence ($t_{max,m}$); the area under the milk level *versus* time curve from 0 to 24 hours after dosing ($AUC_{0\text{-}24,m}$); and the milk: serum ratio per time point (M/S_t), the milk: serum ratio based on AUC (M/S_{AUC}). The average and maximum daily etono-

gestrel dose received by the infant via breast milk ($D_{av,infant}$ and $D_{max,infant}$) were calculated as follows:

$$\frac{D_{av,infant} = C_{av,s} \times M/S_{AUC} \times \text{milk volume}_{\text{ingested over 24 hour}} / \text{body weight}}{D_{max,infant} = C_{max,s} \times M/S_{AUC} \times \text{milk volume}_{\text{ingested over 24 hour}} / \text{body weight}}$$

The average and maximum daily etonogestrel dose were also expressed as a percentage of the daily dose taken by the mother ($D_{\%av,infant}$ and $D_{\%max,infant}$).

Statistical methods

The sample size was based upon an estimated coefficient of variation of about 20% for the quality and quantity variables of lactation at treatment cycle 4. The number of women per treatment group was estimated to be able to reveal a difference of 10% between the treatment groups at the end of the treatment cycle 4. Considering a drop-out rate of 25% and a coefficient of variation of 20%, a sample size of 40 women per group assured a 95% confidence interval of 20% relative to IUCD-means of the lactation variables.

The volume of breast milk was defined as the sum of all feedings in 24 hours, measured by the infant's weight difference from before and after feeding divided by 1.03g/mL (= specific gravity of breast milk). Main parameters, such as breast milk quantity and quality and feeding practices, were analysed for all women who received at least one dose of study medication or had an IUCD inserted (the all-treated group) and the intention-to-treat group, including all women from the all-treated group, except the cases with major protocol deviations. All safety data, including the growth of the children during treatment, were analysed for the all-treated group. Growth at follow up visits was analysed for the intention-to-treat group as some children were seen at times which deviated considerably from the assessment schedule. Follow up visits for which the actual age deviated more than three months from 1.5 and 2.5 years, respectively, were excluded.

Infant growth during treatment was explored using the linear regression model:

$$y_i(t) = a_i + b_i \, age_i(t) + \epsilon_i(t)$$

where the dependent variable $y_i(t)$ is the growth measurement of child i at time t, $age_i(t)$ is the age of the child at time t and ϵ_i the residual error of child i at time t. Analysis of covariance was performed on the summary statistics b_i with the independent variables gender, total duration of treatment (truncated to the last assessment date for the women in the IUCD group), total duration of breastfeeding and treatment of the mother. The adjusted means are presented.

All statistical evaluations were done by means of the SAS system for OS/2, release 6.11. Group comparisons were made by means of descriptive statistics (proc Univariate), regression analysis (proc Reg) and analysis of covariance (proc GLM). Differences in pharmacokinetic parameters between treatment cycles were tested using a two-sided paired t test on log-transformed values, except for $t_{max,s}$ and $t_{max,m}$ for which the signed rank test was applied.

The study was approved by the hospital and medical directorate ethical committees and the Committee on Pharmaceuticals of Iceland.

RESULTS

The study groups and their eventual disposition are shown in Table 1. The all-treated group consisted of 83 women, receiving either desogestrel ($n = 42$) or an IUCD ($n = 41$). A total of 15 women discontinued treatment before the end of treatment cycle 7. In six women discontinuation during the treatment cycle was due to treatment-related adverse experiences. In the desogestrel group five women stopped treatment, one each because of headache and vomiting, diminished lactation, mood changes, bleeding irregularities or perceived increased sweating of the infant. In the IUCD group one woman had her device removed because of mild endometritis. The other women ($n = 9$) discontinued for reasons unrelated to treatment (insufficient compliance). No pregnancy occurred during the treatment period.

The observed drop-out rates were less than the expected 25% in both groups (Table 1) and the actual lengths of 95% confidence intervals were between 4.7% (lactose) and 32.7% (triglycerides) relative to IUCD group means at the end of treatment cycle 4. This means that the sample size was sufficiently large to detect differences of about 10% between the treatment groups.

The main characteristics of the mothers and babies before treatment are shown in Table 2. Treatment groups

Table 1. Disposition of women and infants.

	Desogestrel *n*	IUCD *n*
Women enrolled	42	41
Women treated (AT-group)	42	41
Completed treatment cycle 1	41	40
Completed treatment cycle 4	40	39
Completed treatment cycle 7	33	35
Women discontinued	9	6
Children follow up		
At age 1.5 years		
Available for evaluation	34	34
per protocol group[a]	32	34
At age 2.5 years		
Available for evaluation	20	20
per protocol group[a]	14	13

[a] Actual age did not deviate more than 3 months from 1.5 and 2.5 years, respectively.

Table 2. Characteristics of mothers and newborns before treatment. Values are given as *n*or as Mean (range). IUCD = intrauterine contraceptive device; OC = oral contraceptive.

		Desogestrel		IUCD
Age (years)	29.0	(20–37)	31.2	(23–38)
Height (cm)	169	(159–177)	168	(152–178)
Weight (kg)	68.9	(50–86)	68.0	(54–89)
Parity	2.4	(2–4)	2.5	(2–4)
Menstrual cycle regularity	39		38	
Prior breastfeeding difficulty	11		9	
Previous OC use	41		40	
Previous IUCD use	18		31	
Newborn age (days)	49.1		51.1	
Newborn sex ratio (female:male)	17:25		15:26	
Newborn length (cm)	57.9	(53–63)	58.1	(55–62)
Newborn weight (g)	5283	(4090–6010)	5382	(4175–6910)
Newborn biparietal head circumference (cm)	39.4		39.9	

did not differ significantly with respect to demographic data of mothers and babies, general medical history and menstrual cycle pattern. Other parameters measured before treatment, such as mean blood pressure, heart rate, body mass index and laboratory values (blood chemistry, haematology, urinalysis) did not show significant differences. No clinically significant abnormal laboratory values were observed. Mean milk volume and composition before treatment were also comparable in both treatment groups (Figs 1 and 2).

Figure 1 shows the mean quantity of breast milk in both all-treatment groups measured before treatment and at the end of the first and fourth treatment cycle. There was no difference in the mean volume of milk produced between women using either contraceptive method. The breast milk in both groups had a similar triglyceride, protein and lactose content (Fig. 2). Analysis of the intention-to treat group showed similar results. Most women continued breastfeeding until the end of treatment cycle 7. The percentage of breastfed infants was 97% in the desogestrel and 92% in the IUCD group at the end of cycle 4, but at cycle 7 a slightly higher percentage of the infants (78%) remained breastfed in the desogestrel than in the IUCD group (59%). At all treatment cycles infant growth rate was the same in both groups (Fig. 3).

The pharmacokinetic values measured in the subset of the desogestrel group are shown in Table 3. Based on maximum etonogestrel serum levels in the feeding mother, the milk: serum ratio and on an estimated daily milk ingestion of 150mL/kg[11], it was calculated that the suckling infant received a maximum etonogestrel dose of 0.01–0.05μg/kg/day, i.e. 2.6%–3.7% of the daily maternal dose, corrected for the weight difference between mother and infant.

Two serious adverse experiences occurred (viral meningitis in a woman of the IUCD group and hospitalisation of a newborn for branchial fistula and anal stenosis).

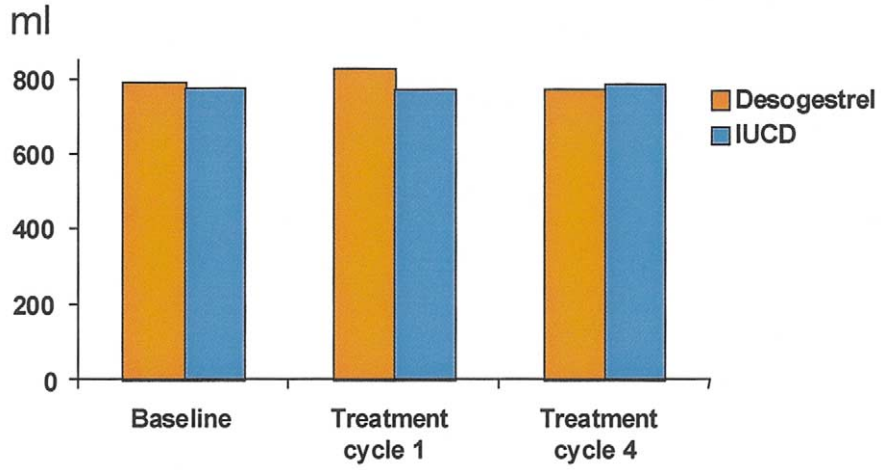

Fig. 1. The effects of desogestrel and an IUCD on the quantity of breast milk (24-hour milk volume) (mean values).

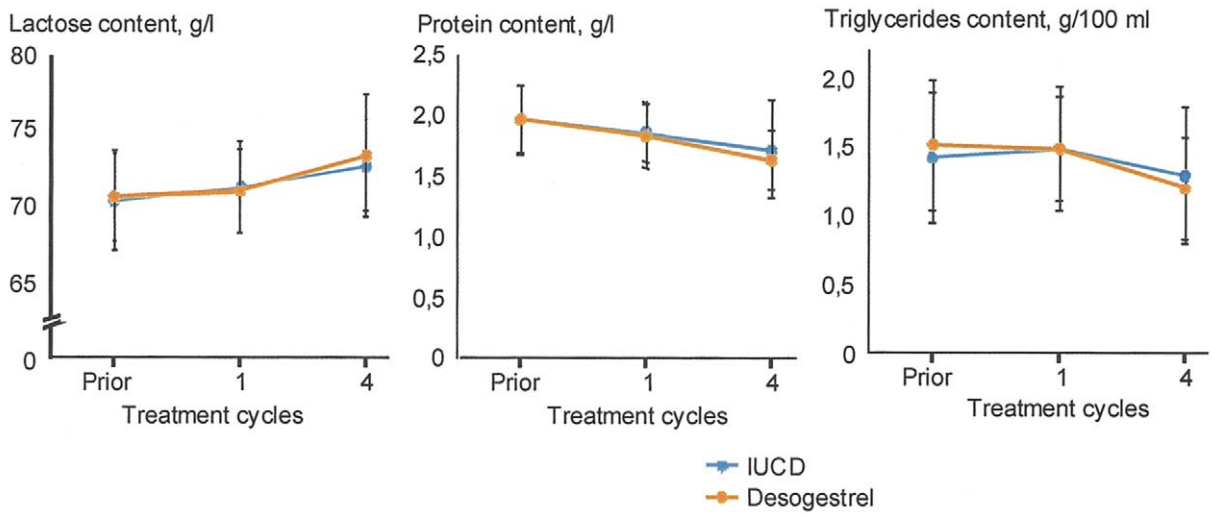

Fig. 2. The effects of desogestrel and an IUCD on milk composition: lactose, protein and triglycerides concentrations (mean values and 95% confidence intervals).

Both were unrelated to the treatment. The overall incidence of possibly or probably treatment-related adverse events for the mothers was higher in the desogestrel group ($n = 6$) than the IUCD group ($n = 2$). This caused discontinuation of treatment in four women of the desogestrel group (one because of bleeding irregularities) and in one woman of the IUCD group. Reported adverse experiences were mild or moderate of character. Among the infants three treatment-related adverse experiences were reported in the desogestrel and none in the IUCD group. Temporary breast enlargement was reported twice and perceived increased sweating in one baby.

Table 4 shows the summary statistics of the growth of the children (intention-to-treat group) at 1.5 and 2.5 years. Clinically relevant differences between both treatment groups were not observed. In the all-treated group there was one child with abnormality of psychomotor development (mental retardation) in the desogestrel group and one in the IUCD group had asthma. One child in the desogestrel group was hospitalised for a viral infections for three days, recovering completely. None of these events were considered to be treatment-related.

DISCUSSION

Globally, breastfeeding is an important and effective means of child spacing. However, uncertainty exists about the extent to which a woman can rely on lactational anovulation for contraception. Breastfeeding alone is not an effective form of contraception, since women may resume normal ovulation while still breastfeeding. During lactational amenorrhea the probability of pregnancy is initially low at around 2%, but increases after

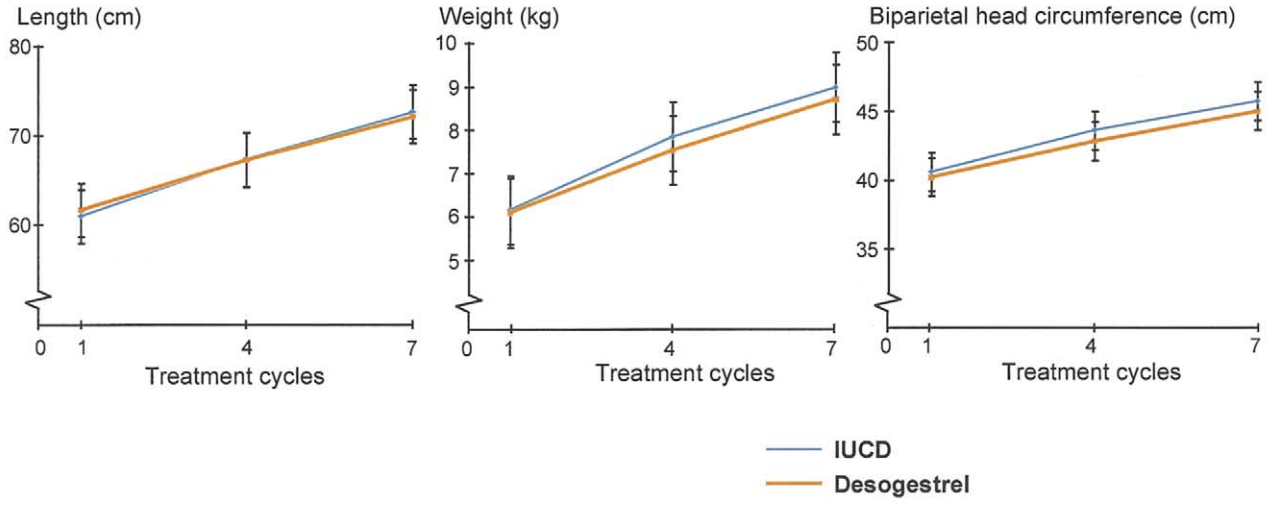

Fig. 3. Growth of newborns of breastfeeding women practicing postpartum contraception with desogestrel or an IUCD.

Table 3. Mean (SD) pharmacokinetic values based on etonogestrel serum and milk levels from a subset of 10 women participating in the desogestrel group.

Parameter	Treatment cycle 1	Treatment cycle 4	Difference between both treatment cycles[a]
$C_{max,s}$ (pg/ml)	602 (166)	538 (220)	NS
$t_{max,s}$ (h)	2.61 (1.41)	3.96 (3.46)	NS
$AUC_{0\text{-}24,s}$ (h.pg/ml)	6539 (2384)	6377 (1744)	NS
$C_{av,s}$ (pg/ml)	272 (99)	266 (73)	NA[1]
$C_{max,m}$ (pg/ml)	203 (113)	314 (251)	NS
$t_{max,m}$ (h)	6.00 (5.54)	5.24 (5.14)	NS
$AUC_{0\text{-}24,m}$ (h.pg/ml)	2347 (865)	3446 (1829)	$P = 0.01$
M/S_{AUC} (ratio)	0.37 (0.11)	0.55 (0.21)	NS
$D_{av,infant}$ (μg/kg/d)	0.015 (0.005)	0.022 (0.011)	NA[2]
$D_{\%av,infant}$ (%)	1.15 (0.42)	1.67 (0.77)	$P = 0.01$
$D_{max,infant}$ (μg/kg/d)	0.034 (0.014)	0.048 (0.038)	NA[3]
$D_{\%max,infant}$ (%)	2.63 (1.09)	3.74 (2.50)	$P = 0.006$

[a] NS = not statistically significant ($P \geq 0.05$); NA = not assessed, [1]same as for $AUC_{0\text{-}24,s}$; NA [2]same as for $D_{\%av,infant;}$ NA [3]same as for $D_{\%max,infant}$.

approximately six cycles postpartum[6]. Once a woman regains her menstrual pattern, contraceptive reliability decreases rapidly and other means of contraception are advisable[6]. This applies particularly when the baby is being weaned and solids gradually introduced. In some populations, such as in the Nordic countries, partial breastfeeding may continue for many months.

The progestogen-only pill offers reliable contraception without oestrogen-related adverse effects on milk production and composition[1,12,13]. Drawbacks of the traditional progestogen-only pills include a lower contraceptive efficacy compared with the combined oral contraceptive pills, an unpredictable bleeding pattern[3], particularly in younger women who are not lactating, and the potential occurrence of dose-related androgenic effects on carbohydrate metabolism, serum lipoproteins and the skin[14]. Desogestrel overcomes most of these disadvantages, since it has a relatively low androgenic activity[15]. A dose that is high enough to consistently inhibit ovulation is not likely to induce androgenic adverse effects[14,16]. In addition, due to ovulation inhibition, the latitude of tablet intake may be longer than with conventional progestogen-only pills, at twelve instead of three hours[7,8].

In Iceland almost all women start breastfeeding their babies and in society the motivation to continue lactation is strong. Women usually have strong personal preferences on what contraception to use. For that reason the study had to be open, allowing women the choice of contraception. Apart from the number of women with previous IUCD experience who tended to choose this again, the two treatment groups appeared to have similar characteristics at study initiation. The administration of 75μg/day of desogestrel did not appear to affect the volume and main nutrient contents of breast milk nor did it affect growth of the breastfed infants. This is in accordance with reports on the effects of other progestogen-only pills during breastfeeding[1,13,17,18].

From the pharmacokinetic data it appeared that only a small amount of etonogestrel enters breast milk. As little as 0.01μg–0.05μg etonogestrel per kg bodyweight per day may be transferred to the infant, based on an estimated milk ingestion of 150mL/kg/day. This is of the same order as reported for other progestogens, such as 2.8% for levonorgestrel[9,19]. The higher etonogestrel concentration recorded in the later stage of lactation (difference between treatment cycles in $AUC_{0\text{-}24}$ values for time curves of etonogestrel milk) was thought to be an artefact as the milk samples were not collected according to a fixed time schedule but on demand. There was also a difference in time of milk collection between cycle 1 and 4. A higher proportion of infants at cycle 4 (being more disturbed by the 16-hour hospitalisation than when they were younger) were being fed more frequently at times coinciding with peak serum etonogestrel levels. As milk samples were taken during every feeding this explains the higher amounts of etonogestrel found in the milk samples at the end of treatment cycle 4. A reduction of infant exposure to etonogestrel could thus be achieved by care-

Table 4. Mean (SD) growth of the children at follow up visits (per protocol group).

	Desogestrel		IUCD	
	1.5 years $n = 32$	2.5 years $n = 14$	1.5 years $n = 34$	2.5 years $n = 13$
Height (cm)	83.3 (3.1)	93.9 (3.5)	83.1 (2.9)	92.5 (3.5)
Weight (kg)	11.1 (1.3)	13.9 (1.3)	11.5 (1.4)	13.1 (1.3)
Biparietal head circumference (cm)	48.5 (1.2)	48.9 (0.5)	48.9 (1.6)	49.8 (1.8)

ful timing of tablet intake in relation to feeding, such as just before the last evening feed.

Measurements of blood pressure did not reveal any clinically significant abnormal values. The physiologically normal weight loss in the cycles following pregnancy and delivery was marked in some women in both groups, but as expected this weight loss ceased by the later observations, at cycles 4 and 7.

The incidence of adverse experiences reported by the mothers was slightly higher in the desogestrel than the IUCD group, mainly consisting of menstrual irregularity and gastrointestinal disorders. These were probably hormonal in character and in line with those recorded previously in women using desogestrel or levonorgestrel[9]. In this study only one woman discontinued desogestrel treatment because of bleeding irregularities. This was to be expected since the women were lactating, but is different from the discontinuation rates usually observed during the use of a progestogen-only pill outside lactation, when bleeding irregularities are more common[3,9,18]. Similar to other progestogen-only pills, the incidence of mood changes, seen in 7% of the desogestrel group, was relatively low compared with the adverse effects of combined oral contraceptives on libido and mood[20]. Among the IUCD users complications were limited to one discontinuation due to infection. While discomfort is experienced at insertion of IUCDs, this appeared to be less noticeable in this group of postpartum women.

Neither treatment had an adverse impact on the health and development of the infants. This is in agreement with previous comparative studies on the use of progestogen-only pills and IUCD during breastfeeding[14,21]. Two infants, both in the progestogen-only pill group, were found to have mild transient breast enlargement. The significance of this unusual effect is unclear. Follow up data confirmed that the administration of desogestrel during lactation did not induce clinically relevant effects on the growth and development of the infants up to the age of 2.5 years. So far, the long term safety of desogestrel use during lactation in the children has not been studied for such an extended period.

The administration of 75μg desogestrel daily is a safe and effective contraceptive method for lactating women. It does not affect the quality and quantity of breast milk to any significant degree nor has it any impact on the growth and development of the breastfed infants up to the age of 2.5 years, a longer follow up than previously reported.

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