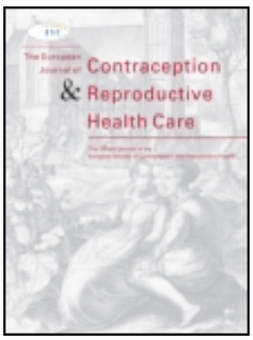

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ORIGINAL RESEARCH ARTICLE

Assessment of the quality of cervical mucus among users of the levonorgestrel-releasing intrauterine system at different times of use

Leticia G. Moraes, Nadia M. Marchi, Ana C. Pitoli, Maria M. Hidalgo, Carolina Silveira, Waleska Modesto and Luis Bahamondes

Family Planning Clinic, Department of Obstetrics and Gynaecology, University of Campinas Medical School, Campinas, Brazil

ABSTRACT

Background and objectives: The quality of cervical mucus (CM) among the levonorgestrel-releasing intrauterine system (LNG-IUS) users is controversial. The objectives were to assess CM compared to the levels of oestradiol (E_2) and the frequency of cycles with luteal activity among users of the LNG-IUS.

Materials and methods: In total, 224 LNG-IUS users for between two months and five years were recruited at a Brazilian family planning clinic. For the cross-sectional part of the study, we enrolled 175 LNG-IUS users at 2, 6 12, 24, 36, 48, and 60 months after insertion (25 women in each group), and we performed one evaluation. For the prospective part of the study, we enrolled 49 LNG-IUS users at the same lengths of use after insertion (7 women in each group), and we evaluated these women once a week for five consecutive weeks.

Results: Mean (± SEM) CM scores of all evaluations among women with single and weekly evaluations were between 3.3 ± 0.9 and 8.5 ± 0.3, respectively independently of the length of use of the LNG-IUS. Mean E_2 values ranged from 45.5 ± 6.8 to 472.5 ± 34.7 pg/ml and the maximum ovarian follicle diameter on the days of evaluation varied from 14.0 ± 1.3 to 31.2 ± 0.4 mm.

Conclusions: The mean CM score of all evaluations, independent of the length of use of the LNG-IUS and normal levels of serum E_2, was below 10 was according to the WHO is inadequate for sperm penetration.

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Cervical mucus; levonorgestrel-releasing intrauterine system; ovulation

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) is one of the most effective reversible contraceptives with a pregnancy failure rate between 0.01–0.3 per 100 woman-years [1,2] and also presents additional non-contraceptive benefits, such as control of heavy menstrual bleeding.[3] Furthermore, many researchers have reported that almost 90% of users were satisfied with this method at the end of the first year after placement.[4–7]

The Mirena-IUS releases 20 μg/day of LNG within the first year of use and approximately 12 μg/day at the end of its lifespan at the fifth year of use.[8,9] Intrauterine levels of LNG are 1000 times higher than plasma levels.[10] This high endometrial concentration of LNG inhibits progesterone and oestrogen endometrial receptors. Although the plasma levels of oestradiol (E_2) correspond to the follicular phase,[11] the endometrium is not responsive to circulating E_2 and the LNG level has an antiproliferative effect, which is responsible for the decidualisation of the endometrium and the reduction of bleeding patterns or amenorrhoea during use.[8] Additionally, LNG induced alterations of the endometrial glycodelin, which could impair the spermatozoa-zona pellucida union, although this is a controversial issue.[12,13]

Despite the large body of evidence regarding the contraceptive effectiveness and non-contraceptive benefits of the LNG-IUS, information about its mechanism of action is scarce. According to the manufacturer,[14] Mirena® prevents pregnancy in several ways: *thickening cervical mucus(CM) to prevent sperm from entering the uterus; inhibiting sperm from reaching or fertilising the egg; thinning the lining of the uterus. Early studies showed inhibition of ovulation through the first year of use*; [15,16] however, long-term users had normal ovarian follicular development,[17] and ovarian cysts or persistent ovarian follicles were also reported.[18,19]

In addition to the described mechanism of action upon the endometrium level and in ovarian follicular development, it was also described changes in the CM and spermatozoa-CM interactions,[14,20,21] although they remain controversial.[15,17] When characteristics of CM and its interactions with spermatozoa were assessed, a significantly higher CM score was found among non-users as compared to users of the LNG-IUS; good sperm penetration was observed only among non-users of the Mirena-IUS.[20] In addition, the CM-spermatozoa interaction was evaluated a few days following the insertion of the LNG-IUS in the middle of the menstrual cycle, and there was both poor CM quality and poor sperm penetration.[21]

Due to the scarce information available on CM quality and ovulatory status among short- and long-term users of the LNG-IUS,[15,17,20,21] the objectives of this study were to assess the quality of CM compared to the levels of E_2 and the frequency of ovulatory cycles among users of the LNG-IUS who used the device for between two months and five years.

CONTACT Luis Bahamondes bahamond@caism.unicamp.br Family Planning clinic, Department of Obstetrics and Gynaecology,University of Campinas Medical School, Caixa Postal 6181, 13084-971 Campinas, SP, Brazil

Materials and methods

Study design and participants

This was a study conducted at the Family Planning Clinic, Department of Obstetrics and Gynaecology, University of Campinas (UNICAMP) Medical School, Campinas, SP, Brazil. The ethical committee approved the study, and all participants signed an informed consent before enrolment. The study was conducted between July 2014 and August 2015.

Users of the 20 μg/day LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) who had used the device for at least two months but no longer than five years were invited to participate. We assessed the women in two different manners. For the cross-sectional part of the study, we enrolled 175 LNG-IUS users at 2, 6, 12, 24, 36, 48, and 60 months after insertion (25 women in each group), and we evaluated these women only once. For the prospective part of the study, we enrolled 49 LNG-IUS users at the same durations of use after insertion (seven women in each group), and we evaluated these women one time each week for five weeks.

Women were included if they had used the LNG-IUS for at least two months but no longer than 60 (± 2) months, were aged 18–45 years old, had not breastfed for at least six months, and had a body mass index (BMI; kg/m^2) < 30. We enrolled 175 women in the cross-sectional part of the study and 49 participants in the prospective part. The CM collection, blood collection, and vaginal ultrasonography were performed in the cross-sectional group when the women came to the clinic for a routine examination. In the prospective group, we performed the same procedures once a week for five weeks.

Procedures

CM evaluation

The CM was collected during a gynaecological examination. The cervix was exposed using a non-lubricated speculum; the external os was cleaned with a swab, and the CM was collected using a small syringe. When the CM was thick or densely adherent, we used a cytobrush or a forceps to collect it. The CM samples were analysed at the same facility within 15 min of collection and were examined both grossly and using a microscope to assess volume, consistency, spinnbarkeit, ferning, and cellularity, as described by the WHO.[22] A CM score higher than 10 out of 15 total points was indicative of CM permitting sperm penetration.

Ovarian follicular development assessment

Transvaginal ultrasound imaging (TVU) was performed to assess the mean diameter of the dominant ovarian follicle (measurement of the two largest perpendicular axes). The mean diameter was the sum of both diameters divided by two. Ovulation was defined by p levels ≥ 3 ng/ml and, when possible, by observation of follicular rupture by TVU.

Hormone determinations

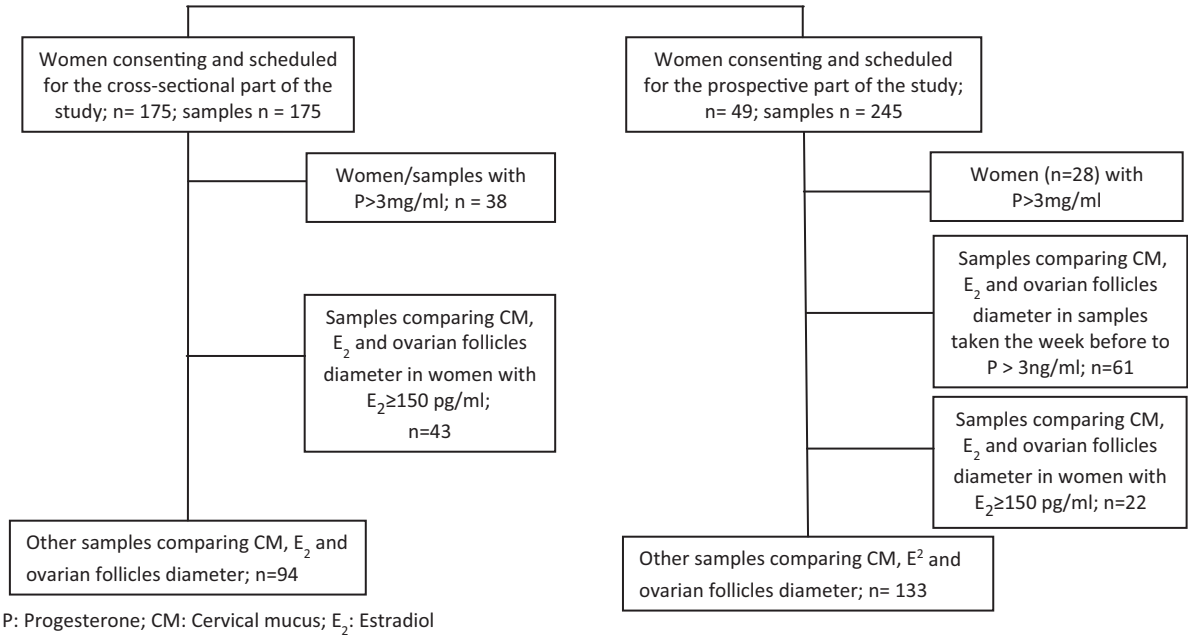
Ten milliliters of blood were collected from a peripheral vein and centrifuged, the serum was frozen and maintained at −20 °C until the hormonal determinations were made. E_2 and p were evaluated in all samples. All determinations were carried out in duplicate using commercial kits (Roche Diagnostics GmbH, Mannheim, Germany).

Analysis of the data

First we identified the number of samples with $p \geq 3$ ng/ml (ovulation or luteal activity) in both groups of women. Next, we evaluated the CM scores and compared them with the E_2 value (< 150 pg/ml or ≥ 150 pg/ml) and also with the mean maximum follicular diameter in all other samples in both groups of women with $p < 3$ ng/ml. Finally, we identified and assessed the samples taken the week before $p > 3$ ng/ml. Figure 1 shows a flowchart with the analysis of samples. All the values are presented as mean ± standard error (SEM).

Results

Some sociodemographic characteristics of the participating women are presented at Table 1. The mean (±SEM) CM



P: Progesterone; CM: Cervical mucus; E_2: Estradiol

Figure 1. Flowchart of the participating women and the assessments performed.

Table 1. Some characteristics of the participants of both groups[a].

Variables	Women with a single evaluation ($n = 175$)	Women with five weekly evaluations ($n = 49$)	p Value
Age (years)	37.4 ± 0.62	35.8 ± 1.02	0.180[c]
Schooling (years)	9.0 ± 0.54	11.0 ± 0.50	<0.001[d]
BMI (kg/m^2)[b]	27.9 ± 0.54	28.8 ± 0.78	0.208[d]
Number of pregnancies	1.6 ± 0.07	1.5 ± 0.16	0.701[d]
Number of deliveries	1.7 ± 0.08	1.4 ± 0.15	0.036[d]

[a]All values are mean ± SEM; [b]BMI: body mass index; [c]Student t-test; [d]Mann–Whitney non-parametric test.

Table 2. Comparison between oestradiol levels, cervical mucus score and ovarian follicle diameter in women with single evaluation according to level of oestradiol[a].

Months of use	N	Oestradiol (pg/ml)	CM score	Ovarian follicle diameter (mm)
Samples with oestradiol <150 pg/ml ($n = 94$)				
2	14	51.7 ± 8.5	4.7 ± 09	28.0 ± 2.5
6	16	69.1 ± 8.2	3.9 ± 0.6	21.4 ± 2.4
12	12	58.4 ± 9.9	4.2 ± 0.4	27.6 ± 2.2
24	17	55.7 ± 5.6	4.6 ± 0.6	17.9 ± 1.5
36	10	45.5 ± 6.8	3.8 ± 0.6	30.6 ± 6.5
48	10	56.6 ± 10.9	3.3 ± 0.9	14.0 ± 1.3
60	14	58.6 ± 9.8	4.7 ± 0.5	24.0 ± 2.7
Samples with oestradiol ≥150 pg/ml ($n = 43$)				
2	8	308.8 ± 35.9	4.7 ± 0.5	29.4 ± 2.8
6	6	472.5 ± 34.7	4.0 ± 0.7	24.7 ± 2.5
12	6	337.5 ± 60.9	5.2 ± 0.6	19.4 ± 2.4
24	6	446.6 ± 62.4	6.8 ± 0.8	23.8 ± 2.1
36	6	240.8 ± 16.3	4.2 ± 0.5	19.4 ± 1.3
48	6	371.2 ± 79.7	8.0 ± 0.7	17.9 ± 2.0
60	6	255.6 ± 25.4	7.3 ± 0.5	16.8 ± 1.2
Samples with progesterone ≥3.0 ng/ml ($n = 38$)				
2	3	106.8 ± 5.0	4.3 ± 0.9	17.2 ± 4.7
6	3	132.4 ± 2.2	1.0 ± 0.7	12.0 ± 2.5
12	7	121.4 ± 26.3	2.3 ± 0.3	12.3 ± 2.4
24	2	230.1 ± 60.4	1.0 ± 1.0	30.0 ± 2.7
36	9	134.5 ± 12.6	2.5 ± 0.6	11.7 ± 0.4
48	9	152.3 ± 15.6	2.1 ± 0.3	7.7 ± 3.6
60	5	87.6 ± 13.6	1.0 ± 0.8	7.7 ± 3.3

[a]All values are mean ± SEM; CM: cervical mucus.

score of all evaluations among women with simple and weekly evaluations was between 3.3 ± 0.9 and 8.5 ± 0.3, respectively independently of the length of use of the LNG-IUS. The mean (± SEM) of the E_2 values ranged from 45.5 ± 6.8 to 472.5 ± 34.7 pg/ml and the maximum ovarian follicle diameter on the same days of evaluation varied from 14.0 ± 1.3 to 31.2 ± 0.4 mm (Tables 2 and 3).

There were 28 women with $p \geq 3$ ng/ml (ovulation or luteal activity) among the women with five weekly evaluations. For the women who underwent five weekly evaluations there was a higher probability of cycles with luteal activity with longer periods of use of the LNG-IUS. In addition, among the group of women with weekly evaluations, 28 women presented $p \geq 3$ ng/ml and among those women in 18 cases there were no identifiable ovarian follicles and in the other 10 cases they presented luteinised unruptured follicles (LUF) (Figure 2). We found there were more cycles with luteal activity after the six months of use.

Table 3 shows the values for the women who participated on the five week evaluations. The analysis was divided on those samples with E_2 values <150 pg/ml and those with E_2 values ≥150 pg/ml and the samples obtained the week before of $p > 3$ ng/ml. Although in some samples we observed mean levels of $E_2 \geq 150$ pg/ml, the mean CM score was in all cases below 10 and ranged from 6.1 to 7.4.

Table 3. Comparison between mean oestradiol levels, the cervical mucus score and ovarian follicle diameter in women with five weekly evaluations[a].

Months of use	N	Oestradiol (pg/ml)	CM score	Ovarian follicle diameter (mm)
Samples with oestradiol <150 pg/ml ($n = 142$)				
2	19	47.9 ± 7.2	5.5 ± 0.5	25.5 ± 3.3
6	21	54.5 ± 11.9	5.0 ± 0.2	22.7 ± 2.6
12	22	75.6 ± 7.5	4.9 ± 1.1	17.4 ± 1.7
24	23	62.6 ± 7.1	5.3 ± 0.4	31.2 ± 0.4
36	23	67.5 ± 0.9	5.8 ± 0.6	18.1 ± 0.2
48	19	52.5 ± 7.9	5.6 ± 0.1	16.7 ± 2.4
60	15	85.2 ± 14.7	5.4 ± 0.5	23.2 ± 3.3
Samples with oestradiol ≥150 pg/ml ($n = 60$[b])				
2	14	406.4 ± 1.8	6.1 ± 0.1	24.7 ± 1.2
6	7	323.6 ± 27.8	6.8 ± 0.7	20.0 ± 0.1
12	8	429.8 ± 67.7	6.5 ± 0.5	19.6 ± 2.8
24	7	286.5 ± 29.4	7.1 ± 0.6	24.7 ± 4.2
36	5	297.1 ± 49.4	6.8 ± 0.9	24.8 ± 0.7
48	6	235.9 ± 31.4	7.4 ± 0.4	17.2 ± 3.5
60	13	408.9 ± 81.9	6.4 ± 0.5	24.8 ± 3.2
Samples on the week before progesterone ≥3 ng/ml ($n = 28$)[b]				
2	1	147.5 ± 4.5	6.0 ± 0.3	17.1 ± 4.3
6	5	354.8 ± 29.6	6.7 ± 1.4	17.7 ± 2.3
12	2	258.8 ± 113.5	6.5 ± 2.5	14.0 ± 3.9
24	4	211.7 ± 72.1	6.5 ± 0.3	19.3 ± 4.6
36	5	103.7 ± 20.4	6.3 ± 0.1	14.0 ± 1.6
48	7	174.7 ± 31.4	8.5 ± 0.3	24.5 ± 1.5
60	4	293.8 ± 109.0	7.7 ± 0.3	18.6 ± 0.3

[a]All values are mean ± SEM; CM: cervical mucus; [b]some samples on the group of the week before progesterone >3 ng/ml were also recorded as oestradiol >150 pg/ml. No any woman who p level reached 3.0 ng/ml or higher is in any of the three groups.

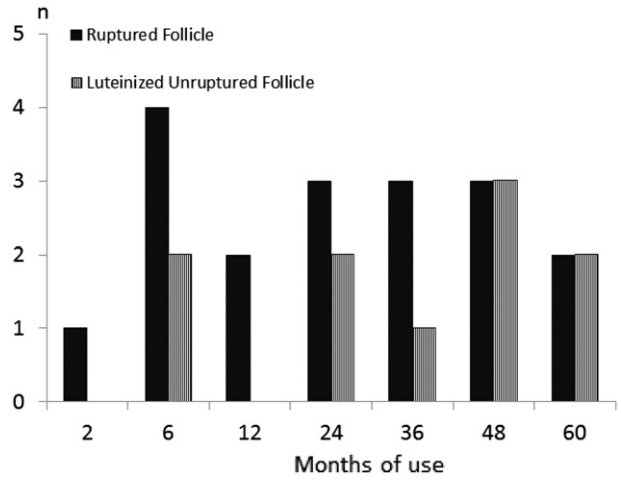


Figure 2. Number of cycles with luteal activity (progesterone ≥3 ng/ml) (28) by duration of use among LNG-IUS users with five weekly determinations ($n = 49$).

Discussion

Findings and interpretation

We observed that the LNG-IUS affects the quality of CM because we did not find a CM score greater than nine according to the WHO definitions [22] in any of the evaluated samples although, the serum E_2 levels corresponded with the follicular phase of the menstrual cycle. A score greater than 10 out of a maximum of 15 is indicative of good CM and favours sperm penetration.[22] Several authors have previously evaluated CM. Two studies [15,17] examined CM in LNG-IUS users during the 4th and 7th year of use and concluded that CM is probably unlike to be a part of the mechanism of action of the device because they observed good CM quality. However, they examined the CM after a long period of freezing and thawing, which goes

against the recommendations of the WHO [22] because this process could alter the quality of the specimen.

Recently, two new studies have examined mid-cycle CM and CM-sperm penetration among users of the 20 μg/day Mirena-IUS who have used the device for more than six months or immediately after insertion.[20,21] The first study [20] showed that in 14 LNG-IUS users and 16 non-users, 14% of LNG-IUS and 69% of non-LNG-IUS users had a CM score $\geq$10 ($p = 0.004$); also LNG-IUS users did not present CM-sperm penetration when compared to non-users (0% vs. 64.3%, $p < 0.001$). The other study [21] analysed CM on days 1, 3, and 5 after Mirena-IUS insertion when it was placed at mid-cycle. At the time of insertion, all participants showed excellent CM scores and sperm penetration; however, from the first day onward, after placement of the device, most of the women presented with poor CM as well as poor sperm penetration.

Our findings are in agreement with two of the studies,[20,21] and they indicated that the use of an LNG-IUS provoked profound changes in the quality of CM. We evaluated CM, E_2, and ovarian follicular development on the same day and one time each week for five weeks to simulate a normal menstrual cycle because we were unable to identify the day of the menstrual cycle due to the menstrual changes induced by the device.[7] During the evaluation, we only considered those CM samples in which p was <3 ng/ml on the same day to avoid any changes in CM that were provoked by the circulating p.

We observed that ferning and cellularity were the two CM properties most affected by the use of the LNG-IUS, while volume, consistency, and spinnbarkeit were less affected. It is well described that ferning and cellularity are affected by the presence of progestogen, such as the LNG released by the evaluated device.[23] Otherwise, we can speculate that the high cellularity observed in CM could be a consequence of irritation provoked by the IUS strings in the cervical canal. In addition, we observed a trend of higher mean CM scores among the women of the prospective study as compared with the women of the cross-sectional group. Nevertheless, it is important to take into account that the E_2 levels were also higher among the women belongs to the prospective group.

Our results also showed that Mirena-IUS users exhibited luteal activity from the sixth month of use through the end of the lifespan of use at 60 months. Furthermore, among women with luteal activity LUF was observed in 24% of the women when the weekly evaluations were performed. However, this finding could be not accurate because one time a week is not adequate to evaluate LUF and it is more appropriate which requires daily evaluation.

In a previous study with 20 women who had used the Mirena-IUS for four years,[24] the authors reported that 75% of the evaluated women presented ovulatory cycles according to their p levels. In addition, in a study that evaluated the pharmacokinetics and pharmacodynamics of the LNG-IUS users up to one year after placement,[16] the authors found that 44.8% of the evaluated cycles showed an ovulatory pattern (ovulation or ovulation with luteal insufficiency); however, the authors did not assess follicular development.

In a similar study conducted amongst women who had used the LNG-IUS for four years,[15] the authors observed that 15 out of 17 evaluated cycles (88%) showed an ovulatory pattern; however, only 8 out of 17 cycles (47%) presented with normal follicular development and rupture upon ultrasonography. In the same study,[17] 15 women were evaluated during the seventh year of LNG-IUS use, and it was observed that 93% of the cycles were ovulatory, but only 58% presented with normal follicular development or rupture. Our study confirmed that when users of the LNG-IUS presented luteal activity, it was associated to disturbed ovarian follicle development and rupture independently of the length of use.

Strengths and limitations of the study

To the best of our knowledge, this is the first study to evaluate the CM quality and ovarian function in a cohort of LNG-IUS users who had used the device for two months to up to five years. The main limitations of the study were that due to the complexity of the procedures, the number of cases was limited and we also did not evaluate CM-sperm penetration. The strengths were the inclusion of women at different times of use and the evaluation of E_2 and follicular development at the same time as a CM evaluation.

Implications for healthcare personnel

Findings of the study could be useful for policy-makers to inform clinicians, users, and potential users about the mechanism of action of the 20 μg/day LNG-IUS.

Unanswered questions and future research

We were unable to evaluate CM-sperm interaction and consequently we failed in the evaluation in one of the proposed mechanisms of action.

Conclusions

Users of the Mirena-IUS presented CM score below 10 which according to the WHO is inadequate for CM-sperm penetration in the majority of users and likely is one of the mechanisms of action of the device. In addition, while many women presented with at least one determination of $p \geq 3$ ng/ml, indicating ovulation or luteal activity, follicular development and rupture are also further mechanisms of action of the LNG-IUS.

Disclosure statement

We declare that we have no conflicts of interest regarding this study. Luis Bahamondes acted occasionally at the Board of Bayer. The other authors declare no conflicts of interest.

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