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Does duration of use of LNG-IUDs vary by contraceptive experience of the provider?

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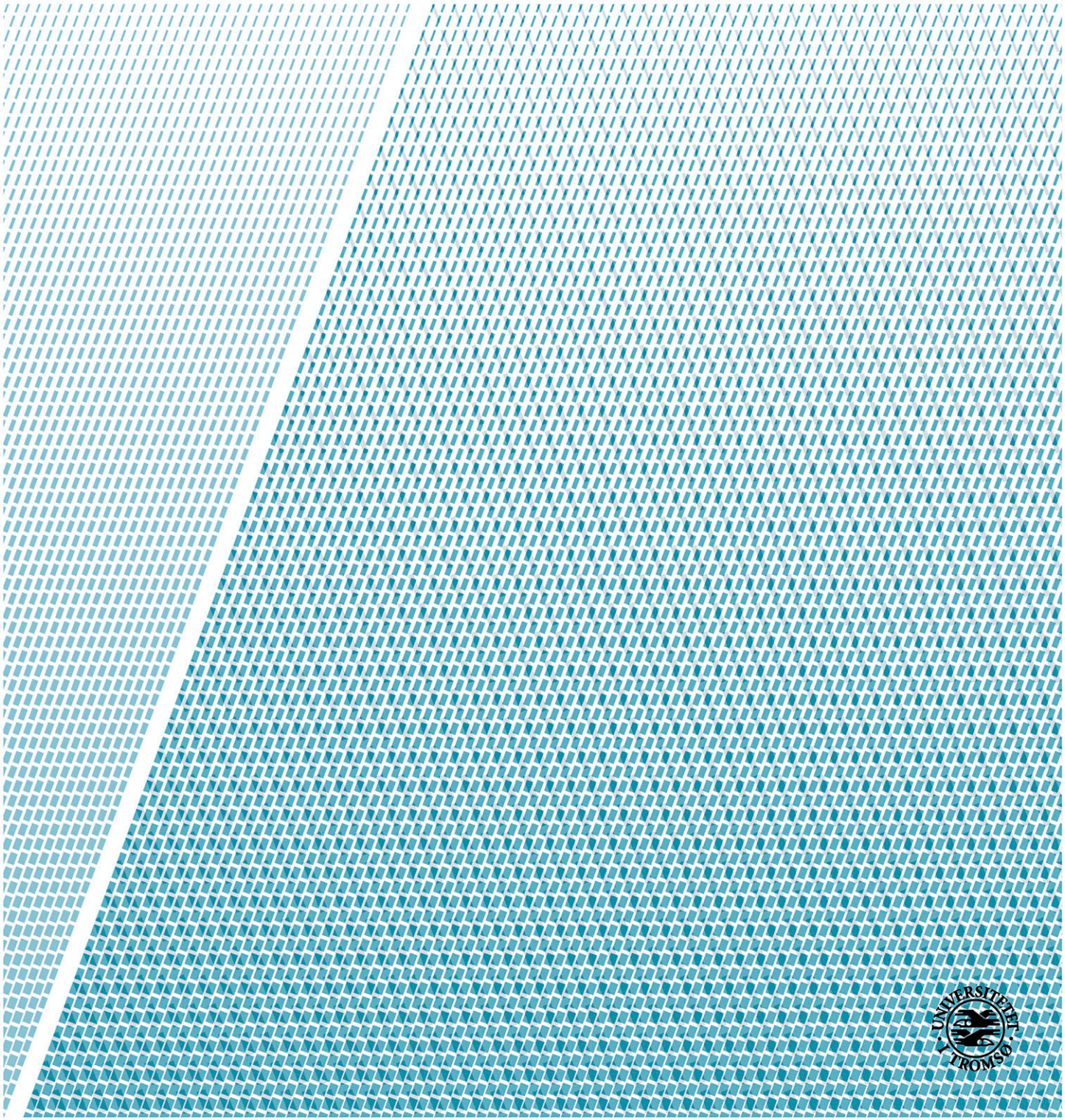
Master thesis in medicine, MED-3950, June 2019



Preface

Women's health is an important topic that I have developed a great interest for during my years in medical school. It was clear to me that I wanted to write my master thesis related to this subject. I was immensely excited when I came in contact with my supervisor, professor Finn Egil Skjeldestad, who suggested that I could write about Norwegian women's use of hormonal IUD and contraceptive implants in relation to the contraceptive experience of the provider. I found this topic interesting and highly relevant for women today who have several choices when it comes to contraceptive methods. Another interesting aspect was that there was little to no literature on this topic, thus there was a possibility that the outcome could provide some new insight.

During the early stages of work, we decided to exclude subdermal implants and only focus on hormonal IUD in the thesis. This way, the use of hormonal IUD in relation to provider could be viewed more thoroughly.

The journey of writing this thesis has been tough and at times frustrating, but most of all a great learning experience. I want to sincerely thank my supervisor, Finn Egil Skjeldestad, who has gained access to data, organized the data file and done the more advanced statistical methods (survival analysis/Cox regression). This thesis could not have been written without his supervision and help.

June 2nd, 2019

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Contents

Abstract

Objective: To evaluate whether duration of LNG-IUD use varies by the contraceptive experience of the provider.

Methods: 49 499 women who had a LNG-IUD prescription during 2010 and 2011 were identified from the NorPD database. The contraceptive experience of the providers was measured as number of prescriptions for any hormonal contraception, and number of LNG-IUD prescriptions in 2008/2009. Duration of use was estimated by survival analysis and Cox regression models were used to predict determinants of discontinuation.

Results: General practitioners and gynecologist had the most experience prescribing LNG-IUDs. Continuous use of the device increased with age and was highest among older women. Providers experience related to number of LNG-IUD prescription before study start did not have an effect on duration of use, neither did providers profession. Young women under the age of 20 had the highest probability to change to another hormonal contraceptive method (Hazard rate 1,97 (95% CI: 1,77 – 2,19)). Women in the age groups 40 – 44 and 45 – 49 were more likely to continue their use of LNG-IUD (Hazard rate 0,96 (95% CI: 0,94 – 0,99) and Hazard rate 0,96 (95% CI: 0,93 – 0,99), respectively). New user and continuous user of LNG-IUD were associated with increased probability for changing to another hormonal contraceptive method (Hazard rate 1,10 and 1,05, respectively).

Conclusion: The duration of use of LNG-IUD did not vary by the contraceptive experience of the provider. Users age, new use and continuous use of the device was significantly associated with duration of use.

Abbreviations

LARC	Long Acting Reversible Contraception
LNG-IUD	Levonorgestrel-releasing Intrauterine Device
COC	Combined Oral Contraceptive
POP	Progestogen-Only Pill

1 Background

Levonorgestrel-releasing intrauterine devices (LNG-IUDs) are long acting reversible contraceptives (LARCs) and have been available in Norway since 1993. Other types of LARCs include copper IUDs and contraceptive implants. The LNG-IUDs are T-shaped and contain gestagens in different quantities. They have a lifespan of three to five years depending on the gestagen content (amount/dose) (1).

LNG-IUDs are associated with a high safety profile and are suitable for a broad range of women regardless of age and parity(2). They have the advantage of not being user- dependent as the contraceptive efficacy is dependent on one single act of insertion. The Norwegian Directorate for Health and Social Affairs recommends that more women should be provided counselling on the different types of LARCs, including hormonal IUDs, because of the high efficacy compared to short acting reversible contraceptive methods (2). LNG-IUDs may especially be suitable and cost-effective for certain groups such as young women who are not planning to have children in the next few years, women who have recently given birth and want space between their pregnancies and parous women who are not planning to become pregnant again.

Studies have shown that LNG-IUDs provide high contraceptive efficacy, with low pregnancy rates reported (3-5). LNG-IUDs are also effective in preventing ectopic pregnancies as they reduce the overall risk of pregnancy to a minimum(3). However, if a contraceptive failure occurs, the possibility of an ectopic pregnancy is somewhat higher, but still low(6) .

The average use of the LNG-IUD has been reported to be between 69,6% and 80,1% after 1 year, and between 33,0% and 46,9% after 5 years (3, 4, 7-11). Most terminations occur during the first year after insertion, and discontinuation rates are reported to be highest among young women, usually under 25 years. After the initial 2 years following insertion, the discontinuation rates decrease (3). Duration of LNG-IUD use and premature discontinuation can be depended on different factors. Two common reasons for premature discontinuation are planning pregnancy and bleeding disturbances.

Bleeding disturbances and oligo-amenorrhea are well known side effects that often occur during the use of LNG-IUDs, and are reasons for early discontinuation among some women(3, 4, 11). Bleeding problems can differ in type depending on duration of use and may

also differ between individuals. Generally, more patients experience spotting and infrequent bleedings during the first initial months of use of LNG-IUDs, whereas oligomenorrhea and amenorrhea are more commonly experienced after the initial three months (3). Counselling on these possible side effects at insertion is important and may reduce premature discontinuation rates (3, 4, 8, 11, 12).

For any contraceptive method, the return of fertility is of importance after termination of any method. For women who want to postpone pregnancy by using a contraceptive method, it is important that the contraception is effective and that it does not reduce fertility after discontinuation. The LNG-IUD has a local and suppressive effect on the endometrium which becomes atrophic and inactive during use of the device (13, 14). Studies have shown a normal return of endometrial function and fertility after removal of the LNG-IUD, and there seems to be no delay in the ability to conceive after removal of the device compared to other contraceptive methods (13, 14).

Difficult and failed insertion of LNG-IUDs have been reported to be low (4, 7, 10, 15). Pain at insertion may occur, but sever pain is reported seldom (4, 16, 17). However, there has been reported higher rates of difficult insertion and pain at insertion related to the Mirena compared to lover dose LNG-IUDs with a narrower insertion tube(16). There has also been described a trend toward easier placement of the smaller LNG-IUDs among nulliparous women, which might be related to the narrower cervical canal in nulliparous women compared to parous women(16).

Over the years there have been conducted many studies with emphasis on users of LNG-IUDs. However, the LNG-IUDs has been on the market for many years, thus the interest for doing research on these devices is now limited. Another reason for the limited interest in research on LNG-IUDs can be the lack of financial support as large clinical trials are costly and time consuming.

There is little, if any, literature at all on contraceptive experience of the providers and if this experience is related to duration of use. The main aim of this thesis is to describe the providers of hormonal IUD prescription in Norway, and to analyse if their contraceptive experience is related to duration of use among women.

2 Purpose of the thesis

To examine whether duration of use of LNG-IUDs varies by contraceptive experience of the provider.

3 Material and methods

In an historical prospective cohort design, we have analyzed data from the Norwegian Prescription Database (NorPD). NorPD was established in 2004, and stores information on redeemed prescription in pharmacies. Through a fictitious number created from the personal identification number given to all Norwegian citizens at birth or upon immigration, the NorPD facilitate data on prescriptions over time denoted users and prescribers. For users, the NorPD includes information on month and year of birth, gender and home municipality. Detailed information about the drugs is also registered. Prescriber information comprises gender, year of birth and graduation, profession, and year and type of medical specialty.

From January 1st, 2004 through June 30th, 2016, the NorPD database comprised 12 729 909 prescriptions denoted 939 469 women. From this database we identified 49 783 women who had a LNG-IUD prescription during 2010 and 2011. After exclusions of women 50 years or older, or age out of range (n=1195), prescriptions to men (n=15), and prescriptions with no information on providers' profession (n=71) nor age (n=3), the study cohort comprised 48 499 women, all having a Mirena device inserted.

We estimated duration of use in months from the date of the first collected LNG-IUD prescription until the date of expiration of the last continuous LNG-IUD prescription, or date of collection of prescription of other hormonal contraceptives. We included women who collected other hormonal contraceptives at the same time or within the first 7 days after an LNG-IUD prescription, as the user obviously intended to start using a LNG-IUD. Use duration for this subset was set to zero months if the user continued to redeem prescription on non-LNG-IUD methods. For women not having prescriptions after study start the duration of use was set to 60 months, or terminated at study end, June 30th, 2016.

At study start, we defined switchers as women who took out a LNG-IUD prescription within 28 days from expiration of the last prescription, if last prescription was combined oral contraceptive, a progestogen-only pill, a vaginal ring or a patch. A time limit was not defined where the last hormonal contraceptive was an implant or a LNG-IUD if the duration were within the expiration window of the prior prescription. A "pause" in use of hormonal

contraception was restricted to women who submitted a LNG-IUD prescription 29 days or later after the most recent collected contraceptive prescription expired. At the study's end, pause denoted women who collected another hormonal contraceptive 180 days or later after expiration of the last dispensed LNG-IUD. Continuous LNG-IUD use was denoted women who collected another LNG-IUD later than 3 years after study start, or within 180 days after the expiration of the device inserted at study start.

At study start we categorized ever users of a LNG-IUD as users with "new use", had used a LNG-IUD but with another hormonal contraceptive method in between as "past use", and women who had an overlapping duration interval from most recent prescription on a LNG-IUD to study start as "continuous use".

User age was categorized as 15-19, 20-24, 25-29, 30-34, 35-39, 40-44 and 45-49 years, whereas prescriber age was categorized as 24-34, 35-44, 45-54, 55-64 and 65-88 years.

Prescribers' profession included general practitioner, gynaecologist, and medical doctors with another speciality. We denoted physicians without specialist status as doctors with "no speciality". This category includes postgraduate students from medical school during their internships, physicians in a residency-training program, and medical students who have valid license issued in the fifth year of medical school. Physicians with more than one speciality were denoted the most recent speciality.

The contraceptive experience of the providers was measured as number of prescription for any hormonal contraception, and number of LNG-IUDs prescriptions over the last two years prior study start (2008/2009) using 40 yearly working weeks as denominator. We categorized experience on prescriptions on hormonal contraception as < 1 a month, ≥ 1 a month, 1-9 a week, and ≥ 10 a week. Accordingly, we categorized prescriptions on LNG-IUD as < 1 per 6 months, < 1 per month and ≥ 1 per month.

All analysis were done in SPSS version 25.0 (IBM Corp., Armonk, NY, USA) with chi-square tests for categorical variables, and *t-test* for continuation variables. Duration of use estimated by survival analysis and Cox regression models were used to predict determinants of discontinuation. All analysis applied a significant level $p < 0.05$. The main exposure was contraceptive experience of provider with duration of use as main outcome.

The board of the NorPD reviewed the protocol and gave permission for use of data. Studies using anonymously data from nationwide registers are by Norwegian legislation exempted from institutional regulatory board approvals and written informed consent from patients.

4 Results:

4.1 Characteristics of providers

In total 6257 medical doctors provided 48 499 LNG-IUD prescriptions in 2010 and 2011. Doctors without speciality (50,5%) and general practitioners (39,4%) were the main providers. We anticipate that the doctors prescribing LNG-IUDs also inserted the device.

Doctors with no speciality were in general younger compared to other providers, with 57% of them in the age group 24 – 34 years (Table 1). General practitioners, doctors with another medical speciality and gynaecologists were older, with a relative even age distribution.

Among medical doctors without speciality, women were in majority and represented 59,4% of them (Table 1). There was a predominance of men among general practitioners and doctors with another speciality. The gender distribution among gynaecologists was somewhat equal, with a slightly higher percentage of men.

As professions, general practitioners and gynaecologists had more experience prescribing hormonal IUDs than doctors without and doctors with other specialities. Whereas nearly 23% of gynaecologists and 17% of general practitioners prescribed monthly LNG-IUDS, only 4% of doctors without speciality and 1% of doctors in other specialities reached this prescription volume.

There was a similar distribution of experience by provider two years before study and in the study. General practitioners and gynaecologist prescribed the most hormonal IUD's during both periods.

General practitioners prescribed a high rate of prescriptions for other hormonal contraception. Around 94% of these doctors prescribed more than one prescription of hormonal contraception a week. In comparison, 52% of gynaecologists prescribed more than 1 prescriptions a week, followed by doctors with no speciality (38,4%).

4.2 Characteristics of users by age

Analysing users by health region, there was a larger distribution of LNG-IUD in East Norway for all age groups (Table 2). The distribution rates were lowest in North Norway. This most likely reflects the number of women in the denominator. Each health region had a more or less steady percentage of prescriptions prescribed to the different age groups.

New use of hormonal IUD was highest among women in the age group 15 – 19 years, and near 99% of young women in this group had never used a LNG-IUD before. New use of hormonal IUD decreased with age. Continuous use of hormonal IUD increased with age and was noticeable higher among older women compared to young women.

The number of women who had not used any contraception prior to the hormonal IUD prescribed during the study, increased with age. The most common previous method of contraception was combined oral contraceptives (COCs) and progestogen-only-pills (POPs), and the use of these contraceptive methods was highest in the youngest age group and decreased with age. Having a pause in the use of contraception was more widespread among young women compared to women in the older age groups. Around 69% of women with age 20 – 24 years compared to around 29% of women with age 45 – 59 years had a pause in their contraceptive use before starting with a LNG-IUD.

As providers, doctors with no speciality were the main providers for LNG-IUD prescriptions for women in the two youngest age groups. Young women also had more frequently young doctors with age between 24 – 34 years as prescribers. In comparison, general practitioners were the main providers for women older than 24 years, and doctors who were 45 years or older prescribed more often to "older" women.

A majority of women between age 15 – 39 years did not have the same medical doctor as provider for most recent contraceptive prescription before study start. The youngest age group (15 – 19 years) had the highest percentage (68%) of women with a different provider. In the two oldest age groups, there was nearly an even distribution of women who had the same doctor and did not have the same doctor for most recent contraceptive prescription prior to study start.

4.3 Duration of LNG-IUD use

Providers experience related to number of LNG-IUD prescription before study start did not have a significant effect on duration of use of hormonal IUD, neither did providers profession.

(Table 3). Users age and previous use of hormonal IUD had a significant effect on the duration of use of LNG-IUD. Young women under 20 years had the highest risk for switching to another hormonal contraceptive method (Hazard rate 1,97 (95% CI: 1,77 – 2,19)). Women between 20 – 34 years in the following three age groups also had a higher probability of changing to another hormonal contraceptive method. Women between 40 – 49 years were more likely to continue the use of hormonal IUD (Hazard rate 0,96). New use and continuous use of LNG-IUD were associated with increased probability to change to another hormonal contraceptive method (Hazard rate 1,10 and 1,05 respectively). Past use of LNG-IUD did not have a significant effect on duration of use of the device.

Figure 1 shows that the cumulative probability of change to another hormonal method (discontinuation rate) by age was highest among young women between 15 – 19 years and decreased with age. For all age groups the probability to change to another hormonal contraception increased with duration of use.

5 Discussion:

As professions, general practitioners and gynecologist had the most experience prescribing hormonal IUDs, and these two groups prescribed the most LNG-IUDs two years before study and in study. Continuous use of hormonal IUD increased with age. Users age and ever use of hormonal IUD had a significant effect on the duration of LNG-IUD use. Providers experience related to LNG-IUD prescriptions did not affect the duration of use.

The cumulative probability of change to another hormonal method was highest among young women. Continuous use of LNG-IUD increased with age, and older women were less likely to switch to another hormonal contraceptive method compared to younger women. These findings are in line with previous studies where young women have the highest premature discontinuation rates(3, 4).

Discontinuation during the first months after insertion were also highest among young women. These discontinuations are most likely caused by difficulties related to insertion. Young, nulliparous women have a narrower cervical canal compared to parous women, which possibly can make the insertion of LNG-IUDs more difficult in these women. Lower dose LNG-IUDs with a smaller insertion tube diameter compared to the Mirena, have been described as easier to insert in nulliparous women(16).

The LNG-IUD is also used as treatment for heavy menstrual bleeding and in menopausal hormone replacement therapy to avoid endometrial hyperplasia due to estrogen stimulation(15, 18-20). The menopausal transition leads to irregular bleeding cycles and in some women may cause menorrhagia. The high rates of LNG-IUD use and continuous use among older women at perimenopausal age can therefore partly be due to climacteric reasons and not only for contraceptive purpose.

In this study we are using the switch to another hormonal contraceptive method as a measurement for discontinuation. Therefore, women who discontinue their use of LNG-IUD without switching to another hormonal contraceptive method, for example because of planning pregnancy, are not reported. This action may underestimate the total number of terminations.

On the other hand, women who experience bleeding disturbances with the LNG-IUD might also use oral contraceptive pills simultaneously to cope with this side effect. These women are reported with discontinuation of LNG-IUD use because of their use of an oral contraceptive pill. Thus, there might be women continuing in the study, who still use the LNG-IUD, but are denoted as quitters due to their start of using oral contraceptive pills.

To estimate the contraceptive experience of the provider, we have used the number of LNG-IUD prescriptions prescribed two years before study start and also assumed that the prescriber inserted the device. Although this might be true in many cases, it is possible that the prescriber and inserter of the device are different persons. Therefore, the number of IUD prescription may provide an estimation of providers experience related to insertion, but it is not an accurate measurement in this case.

6 Conclusion

Duration of LNG-IUD use did not vary by the contraceptive experience of the provider. Age, new use and continuous use of LNG-IUD was significantly related to duration of use of the device. The probability to switch to another hormonal contraceptive method was highest among young women and decreases with age. Older women were more likely to continue their use of the LNG-IUD. New use and continuous use of LNG-IUD were associated with increased probability of changing to another hormonal contraceptive method. Past use of LNG-IUD did not have a significant effect on duration of use of the device

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8 Tables

Table 1 Characteristics of providers (%)

	Profession provider				
	No specialty	**General practitioner**	**Other medical specialty**	**Gynecologist**	**In total**
	N=3159	N=2464	N=214	N=420	N=6257
Age					
24-34	**57,8**	1,0	1,4	1,0	29,7
35-44	**27,1**	22,4	24,8	23,6	24,9
45-54	7,8	32,3	38,8	33,8	20,2
55-64	5,5	37,7	23,4	26,7	20,2
65-88	1,9	6,5	11,7	15,0	4,9
Sex					
Male	**40,6**	66,6	67,8	49,5	52,4
Female	**59,4**	33,4	32,2	50,5	47,6
N prescriptions of hormonal contra-ception last 2 yrs. before study start					
< 1 per month	42,8	1,7	55,1	23,1	25,7
≥ 1 per month	16,6	3,5	13,1	24,8	11,9
≥ 1 per week	40,6	**94,8**	31,8	**52,1**	62,4
N prescription of LNG-IUD last 2 yrs. before study start					
< 1 per 6 months	70,0	24,3	77,6	41,7	50,3
≥ 1 per 6 months	25,7	**58,1**	21,0	**34,5**	38,9
≥ 1 per month	4,3	**17,6**	1,4	**23,8**	10,8
N prescription of LNG-IUD in study					
< 1 per 6 months	56,8	26,5	69,2	43,6	44,4
≥ 1 per 6 months	38,5	**58,0**	28,0	**32,4**	45,4
≥ 1 per month	4,7	**15,5**	2,8	**24,0**	10,2

Table 2 Characteristics of users by age (%)

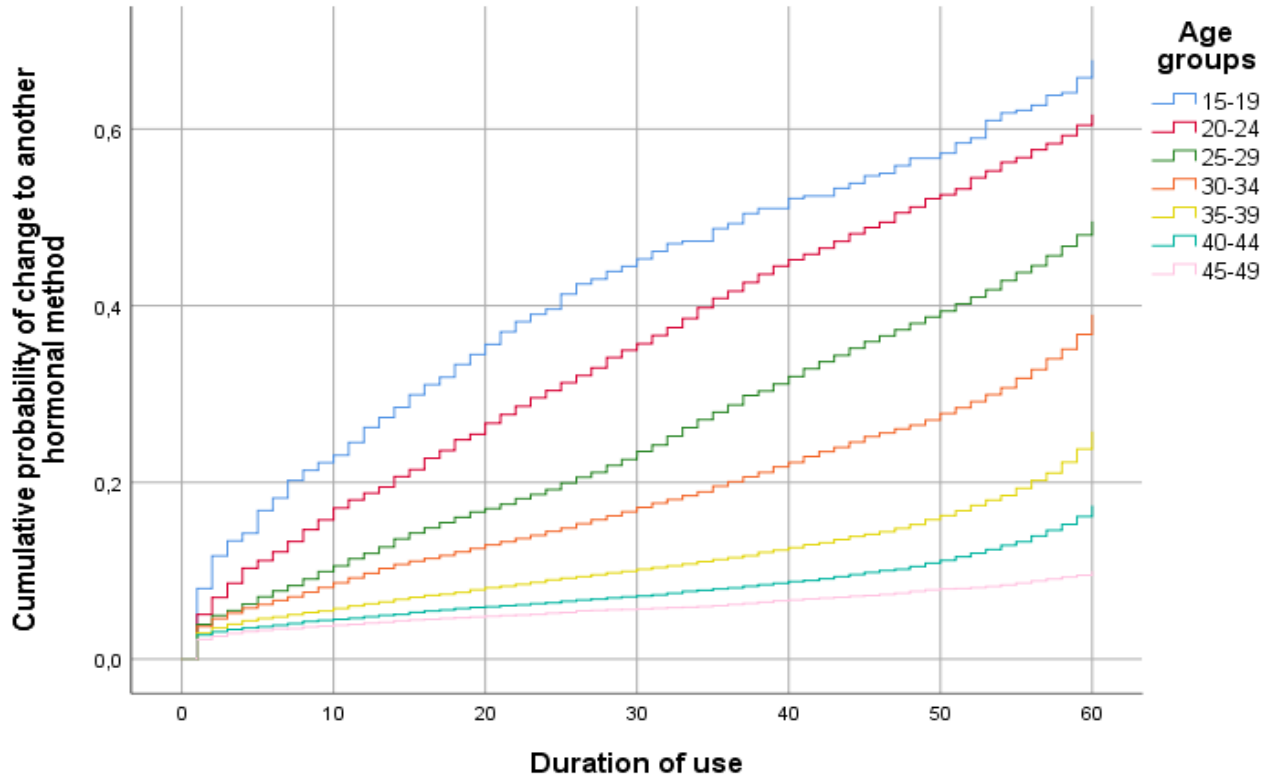
	Users age (years)							
	15-19	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**In total**
	N=351	N=2449	N=5381	N=9037	N=12170	N=12219	N=6892	N=48499
Health region								
East Norway	47,3	44,4	46,7	50,7	51,5	49,8	51,7	50,1
Vest Norway	24,2	25,8	26,9	25,4	24,2	24,5	22,9	24,7
Central Norway	13,7	15,9	15,8	14,5	14,4	15,5	15,2	15,1
North Norway	14,8	13,9	10,6	9,3	9,8	10,1	10,1	10,2
Ever use of hormonal IUD								
New use	99,4	94,2	86,4	76,2	60,6	50,2	49,9	64,2
Continuous use	0,6	3,9	9,1	16,4	27,3	33,8	30,9	24,0
Past use	0	2,0	4,5	7,5	12,1	16,0	19,2	11,8
Continuous use from								
No previous use	12,0	8,0	12,1	15,3	23,3	32,2	39,9	24,3
Pause	60,4	69,4	64,1	55,7	38,6	28,3	25,9	41,9
COC	13,1	7,1	4,5	4,1	4,3	2,5	1,5	3,6
POP	8,5	7,3	8,0	6,5	4,6	1,8	0,9	4,3
Patch	2,0	0,7	0,3	0,2	0,2	0,1	0,1	0,2
Vaginal ring	0,9	1,1	0,6	0,5	0,4	0,2	0,2	0,4
DepoProvera	1,7	1,1	0,7	0,6	0,8	0,7	0,5	0,7
Implants	0,9	1,4	0,5	0,7	0,6	0,3	0,2	0,5
Hormonal IUD	0,6	3,9	9,1	16,4	27,3	33,8	30,9	24,0
Profession provider								
No specialty	47,6	47,5	42,4	35,7	31,7	28,1	26,2	32,9
General pract.	35,0	41,6	44,0	49,0	50,8	50,1	46,2	48,3
Other medical sp	0,9	1,8	1,8	1,5	1,6	1,6	1,5	1,6
Gynecologists	16,5	9,1	11,7	13,8	15,8	20,2	26,1	17,2
Provider sex								
Male	47,6	44,0	44,2	43,7	46,1	47,6	48,3	46,0
Female	52,4	56,0	55,8	56,3	53,9	52,4	51,7	54,0
Provider age (yrs.)								
24-34	29,6	27,8	23,3	17,6	14,3	12,8	11,5	15,9
35-44	23,9	29,5	29,0	28,4	24,6	20,8	19,3	24,3
45-54	24,2	20,7	24,5	27,7	30,3	31,7	29,6	28,9
55-64	17,4	18,7	18,9	21,8	25,5	28,3	31,2	25,2
65-88	4,8	3,3	4,2	4,6	5,3	6,5	8,4	5,7
Provider most recent prescription prior study								
No previous prescriptions	12,0	8,0	12,1	15,3	23,3	32,2	39,9	24,3
Not same MD	68,1	62,6	54,7	48,8	41,8	34,6	30,0	42,3
Same MD	19,9	29,4	33,2	35,9	34,9	33,1	30,1	33,4

Table 3 Probability to change to another hormonal contraceptive method

Profession provider	**Hazard Rate**	**Lower 95% CI**	**Higher 95% CI**
No specialty	1,01	0,99	1,04
General practitioner	1,00		
Other medical specialist	1,02	0,95	1,10
Gynecologists	0,99	0,97	1,02
Age user (years)			
< 20	1,97	1,77	2,19
20-24	1,70	1,63	1,78
25-29	1,37	1,32	1,41
30-34	1,17	1,14	1,21
35-39	1,0		
40-44	0,96	0,94	0,99
45-49	0,96	0,93	0,99
Ever use of hormonal IUD			
New use	1,10	1,08	1,13
Continuous use	1,05	1,01	1,08
Past use	1,0		
Hormonal IUD experience inserter (average no. prescriptions hormonal IUDs 2008-09)			
< 1 per 6 months	1,01	0,99	1,04
≥ 1 per 6 months	1,00	0,98	1,03
≥ 1 per months	1,0		

9 Figures

Figure 1 Cumulative probability of change to another hormonal contraceptive method



10 GRADE-evaluation

<table>
<tr><td colspan="3">Referanse: Sivin I, el Mahgoub S, McCarthy T, et al: Long.-term contraception with the levenogestrel 20 mcg/day (LNg 20) and copper T 380Ag intrauterine device: a five-year randomized study. Contraception 1990;42:361-378.</td><td>Design: RCT
Grade: ★★★★</td></tr>
<tr><td>Formål
Sammenligne bruken av LNG-IUD og kobber spiral (TCu 380Ag) over 5 år i en randomisert studie.

Konklusjon
Få graviditeter ved bruk av begge typer spiral. LNG-IUD hadde signifikant høyere termineringsrate hovedsakelig pga utstøting og amenore, signifikant lavere termineringsrate for andre menstruasjonsproblemer og smerter, og totalt en lavere kontinuasjonsrate hovedsakelig pga amenore.

Land
Brazil, Chile, Dominican Republic, Egypt, Singapore, USA.

År data innsamling
1981–1986, oppfølging frem til 1989.</td><td>Inkludert: Fertile kvinner alder 18–38 år.

Ekskludert:
Kontraindikasjoner mot kobber eller hormonspiral, PID etter siste graviditet og ektopisk graviditet.

Oppfølging: 1, 3, 6 og 12 mnd etter innsettelse. Hvert halvår deretter med gynekologisk us.

Randomisering utført ved bruk av lineær kongruent algoritme. Spiral ble pakket i nummerert konvolutt i henhold til randomisering, og ble åpnet rett før innsettelse.

Datagrunnlag:
LNG-IUD: n= 1124
TCu 380Ag: n = 1121

Eksponeringsvariabler:
Ingen signifikant forskjell mellom gruppene mtp alder, paritet, antall mnd siden siste graviditet, ønske om flere barn, tidligere brukt IUD, PID før siste graviditet, Hb, menstruasjonsblødning dager.

Viktige konfunderende faktorer:
Ingen.

Statistiske metoder:
Aktuarisk livstabell (Tietze), modifisert av Jain og Sivin.</td><td>5-års kontinuasjonsrate:
LNG-IUD: 33,0 per 100
TCu 380Ag: 40,6 per 100
(P<0,001)
Amenore hos LNG-brukere hovedårsak til ulik kontinuasjonsrate.

Gross kumulativ graviditet over 5 år:
LNG-IUD: 1,1 +-0,5 pr 100
TCu 380Ag: 1,4 +-0,4 pr 100
Ingen signifikant forskjell mellom de to gruppene.

<u>Expulsion:</u>
Høyest 1. år etter innsettelse for begge typer spiral.
<u>Expulsion fra 2.-5.år, kumulativ rate:</u>
LNG-IUD: 5,9 +-1,0 per 100
TCu 380Ag: 1,9 +-0,5 per 100
(P<0,05)

Kumulativ 5-års rate, fjerning pga:
<u>Amenore:</u>
LNG-IUD: 19,7 +-1,6 per 100
TCu 380Ag: 0,4+-0,2 per 100

<u>Andre menstruasjonsproblemer:</u>
LNG-IUD: 15,4 +- 1,4 per 100
TCu 380Ag: 23,3 +-1,6 per 100
(P<0,01)

Los to follow-up over 5 år:
LNG-IUD: 127 (11,3%)
TCu 380Ag: 186 (16,8%)</td><td>Sjekkliste:
• Er formålet med studien klart formulert? Ja
• Ble utvalget fordelt til de ulike gruppene med randomiseringsprosedyre? Ja
• Ble alle deltakerne gjort rede for på slutten av studien? Ja
• Ble deltakere/studiepersonell blindet mht gruppetilhørighet? Deltakere ble blindet
• Var guppene like ved starten? Ja
• Ble gruppene behandlet likt? Ja
• Hva er resultatene? Få graviditeter ved bruk av begge typer spiral. Flere som avslutter bruk av LNG-IUD hovedsakelig pga amenore.
• Kan resultatene overføres til praksis. Ja
• Ble alle utfallsmål vurdert? Ja
• Er fordelene verdt ulemper/kostnader? Ja
• Annen litteratur som styrker resultatene? Ja
• Har resultatene plausible forklaringer? Ja

Styrker:
- RCT-studie
- Mange deltakere
- Like grupper ved studiestart

Svakheter: Ingen klare svakheter.</td></tr>
</table>

Referanse: Kerstin Andersson, Viveca Odlind, Göran Rybo; *Levenorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: A randomized comparative trial.* Contraception 1994;49:56-72	**Design:** RCT Grade: ★★★

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer
Sammenligne LNG-IUD og Nova T over 5 års bruk i en RCT-studie. **Konklusjon** Ved bruk av LNG-IUD er det lav graviditetsrate, liten forekomst av PID, redusert menstruasjons blødning og økt Hb. LNG-IUD er derfor å foretrekke som prevensjonmet ode. **Land** Danmark, Finland, Norge, Sverige og Ungarn. **År data innsamling** 1982-1989	**Inkludert:** Friske kvinner, alder 18-38 år, minst 1 tidligere graviditet, villig til indusert abort ved ikke-planlagt graviditet med LNG-IUD, pga mangelfull kunnskap om teratogen effekt. **Ekskludert:** Tidligere ektopisk graviditet, ammer, bruk av injiserbare steroidhormoner som prevensjon de siste 12 mnd. **Datagrunnlag:** LNG-IUD: n = 1821 Nova T: n = 937 Gruppene var like mtp alder og paritet. IUD innsatt 3-10 dager etter menstruasjonsstart, evt i forbindelse med abort i 1. trimester. Oppfølging etter 3 og 12 mnd, deretter årlig opptil 5 år. Kvinner oppfordret til å notere blødningsmønster de første 12 mnd i spesielt designet tabeller. **Eksponering:** Innsettelse av LNG-IUD eller Nova T IUD. **Utfall evaluert:** Kontinuitet, graviditet og utstøtning. Diskontinuitet grunnet blødningsforstyrrelser, amenore, smerter, PID, andre medisinske og personlige årsaker, hormonelle og subjektive bivirkninger. Planlegging av graviditet- Effekt på Hb og vekt. **Statistiske metoder:** BMDP, livstabell for graviditet og diskontinuering (Tietze & Lewit).	**Antall som fullførte 5 år:** Nova T: 315 kvinner (44,5%) LNG-IUD: 736 kvinner (46,9%) **"Lost to follow up":** Nova T: 133 kvinner (14%) LNG-IUD: 115 kvinner (6,3%) **5-års kumulativ graviditetsrate:** Nova-T: 5,9 LNG-IUD: 0,5 P <0,001 **Kumulativ rate fjerning pga blødningsforstyrrelser:** Nova T: 20,7 LNG-IUD: 13,7 (P < 0,01) Signifikant flere fjernet Nova T grunnet kraftig menstruasjonsblødning og forlenget blødning. **Kumulativ rate fjerning pga amenorrhea:** Nova T: 0,0 LNG-IUD: 6,0 (P < 0,001) **Kumulativ rate fjerning pga PID:** Nova T: 2,2 LNG-IUD: 0,8 (P < 0,05) Signifikant økt forekomst av PID blant kvinner ≤ 25 år med Nova T sammenlignet med LNG-IUD. **Hormonelle bivirkninger:** Nova T: 2,0 LNG-IUD: 12,1 (P < 0,001)	**Sjekkliste:** • Er formålet med studien klart formulert? ***Ja.*** • Ble utvalget fordelt til de ulike gruppene med randiseringsprose-dyre? *Randomiseringsprosedyre ikke beskrevet.* • Ble alle deltakerne gjort rede for på slutten av studien? ***Ja.*** • Ble deltakere/studieperson ell blindet mht gruppetilhørighet? *Nei.* • Var guppene like ved starten? *Forskjell i størrelsen på gruppene.* • Ble gruppene behandlet likt? ***Ja*** • Kan resultatene overføres til praksis? ***Ja.*** • Ble alle utfallsmål vurdert? ***Ja.*** • Har resultatene plausible forklaringer? ***Ja.*** • Annen litteratur som styrker resultatene? ***Ja.*** **Styrke:** • RCT-studie. • Mange deltakere. • Tar hensyn til flere relevante utfallsmål. **Svakhet:** • Randomiseringsprosedyre ikke forklart. • Ulik størrelse på de to gruppene. • Pasienter ikke blind

Referanse: Tiina Backman, Sakke Huhtala, Riitta Luoto, Juhani Tuominen, Ilkka Rauramo and Markku Koskenvuo; *Advance Information Improves User Satisfaction With the Levonorgestrel Intrauterine System.* Obstetrics & Gynecology 2002;99:608-613	**Design: Pasientserier** Grade: ★

Formål	**Materiale og metode**	**Resultater**	**Diskusjon/kommentarer**
Se på påvirkning av avansert informasjon som gis om LNG-IUD og effekt på pasienttilfredshet. **Konklusjon** Info som gis ved innsettelsestidspunkt er sterkt assosiert med økt brukertilfredshet blant brukere av LNG-IUD. Assosiasjon mellom info og brukertilfredshet var sterkest mtp muligheten for bortfall av menstruasjon. **Land** Finland **År data innsamling** 1990-1996	**Populasjon:** Alle kvinner som fikk innsatt LNG-IUD i Finland mellom 1990-1993 ble spurt om å delta i studien. 26 630 kvinner ble med. I 1996 ble spørreskjema med 75 spm sendt til 23,885 kvinner. Etter 3 påminnelser ble 75% av skjemaene fylt ut. Usignerte skjema og der fødselsdato ikke stemte med personnummer ble ekskludert (n=554). Antall skjema som ble analysert var 17 360. Gjennomsnittsalder var 40 år (standardavvik 6,4). 99,3% hadde født barn, 78,1% hadde født to eller tre. 83% av kvinnene var gift eller i samboerskap. 23% hadde gjennomgått spontan eller indusert abort. 4,8% hadde tidligere ektopisk gravditet. **Utfall – hoved utfall:** Hvor fornøyd brukerne var med LNG-IUD og hvor mye info de hadde fått om prevensjonsmetoden før innsettelse. **Statistiske metoder:** SAS software 8,0 Kumulativ logistisk regresjonsnalayse basert på femtrinns-skala for tilfredshet som avhengig variabel. OR beregnet med gruppen som mottok svært lite info som referanse, justert for relevante symptomer og alder.	74% kvinner svært eller ganske fornøyd med LNG-IUD. 8,3% kvinner ved svært eller ganske misfornøyd. Brukertilfredshet økte med alder. Brukertilfredshet varierte ikke betydelig med utdanning, sivilstatus, paritet, tidligere prevensjon, røyking og alkohol, Mye info om: - Blødningsforstyrrelser og svært fornøyd: OR = 3,28 (95% KI, 2,61 – 4,10). - Total/tidvis bortfall av menstruasjon og svært fornøyd: OR = 4,96 (95% KI, 4,15-5,93) - PID og fornøyd: OR = 2,52 (95% KI, 2,24 – 2,82). - Risiko for graviditet og fornøyd: OR = 2,27 (95% KI, 1,99 – 2,59) - Fet hud/hår og svært fornøyd: OR = 2,35 (95% KI, 2,09 – 2,65) - Humørsvingninger og svært fornøyd: OR = 2,32 (95% KI 2,06 – 2,61)	**Sjekkliste:** • Er formålet klart formulert? *Ja.* • Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? *Ja.* • Var inklusjonskriteriene klart definert? *Ja.* • Var alle pasientene i samme stadium av sykdommen? *Nei* • Var responsraten høy nok? *Ja.* • Frafallsanal? *Nei* • Ble det brukt objektive kriterier for å vurdere/validere endepunktene? *Nei.* • Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet? *Kun 1 pasientserie.* • Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design/anal? *Ja, men ikke justert for brukervarighet.* • Var registreringen prospektiv? *Nei.* • Kan resultatene overføres til praksis? *Ja.* • Annen litteratur som støtter resultatene? *Ja.* **Styrke:** Stor studiepopulasjon **Svakhet:** Spørreundersøkelse er basert på pasientenes hukommelse 3-6 år tilbake i tid. Ikke justert for brukervarighet.

Referanse: Michael Cox, John Tripp, Sarah Blacksell: *Clinical Performance of the levenorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network: 5-year report.* J Fam Plan Reprod Health Care 2002;28:73-7	**Design:** Pasientserier Grade: ★

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer
Fastslå effekten av LNG-IUS blant britiske kvinner ved bruk over 5 år. **Konklusjon** Det er behov for rådgivning til kvinner ang tidlig blødningsproblemer inkl mulighet for oligomenore og amenore. Dette anses som viktig for kontinuasjon slik at kvinner kan oppleve langtidsfordelene. **Land** Storbritannia **År data innsamling** 1992 – 2000	**Inkludert:** Kvinner 18 – 45 år, som tidligere har født, frisk, normal menstruasjonssyklus. LNG-IUS innsatt mer enn 6 uker etter fødsel. N= 678 **Ekskludert:** Kvinner > 45 år, nulliparous, innsettelse nr 2 eller mer, akuttprevansjon, gravid ved innsettelse, mindre enn 6 uker etter fødsel, samtidig bruk av POP, COC, HRT, pessar, spermisid. **Oppfølging:** 3 mnd, 12 mnd og årlig deretter opptil 5 år. **Utfall:** Vurdere effekten av LNG-IUS: Graviditet, utstøting, perforasjon. Fjerning grunnet blødningsforstyrrelser, smerter, PID, planlegging av graviditet, andre medisinske årsaker, andre årsaker. Kontinuasjonsrate. **Statistiske metoder:** Livstabell. Ugunstige hendelser klassifisert etter WHO definisjoner.	**Gross kumulativ rate 5-års bruk:** Graviditet: 1,0 (95% KI, 0,3 – 2,4) Utstøtning: 5,9 (95% KI, 3,9 – 7,9) **Gross kumulativ 5-års rate, fjerning grunnet:** - Blødningsforstyrrelser og smertefull blødning: 16,7 (KI 95%, 13,3 – 20,0). Over halvparten grunnet kontinuerlig/persisterende blødninger. - Smerter: 4,3 (95% KI, 2,4 – 6,2) - PID: 1,2 (95% KI, 0,4 – 2,5) - Andre plager assosiert med IUS: 20,8 (95% KI, 17,0 – 24,7). Flest grunnet oligo/amenore. - Andre årsaker: 15,0 (KI 95%, 11,3 – 18,7) - Planlegging graviditet: 14.3 (95% KI 10,7-17,9) - Medisinsk ikke-relatert årsak: 4.2 (95% KI, 2,1 – 6,2)	• Er formålet klart formulert? Ja • Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe? Usikkert. • Var inklusjonskriteriene klart definert? Ja • Var alle pasientene i samme stadium av sykdommen? Ja, minst 6 uker postpartum. • Var responseraten høy nok? Ja. • Frafallsanal.? Nei • Ble det brukt objektive kriterier for å vurdere/validere endepunktene? Ja. • Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet? Kun 1 pasientserie. • Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design/anal? Ja • Var registreringen prospektiv? Ja. • Var oppfølgningen lang nok? Ja. • Var oppfølgningen tilstrekkelig for å nå endepunktene? Ja. • Kan resultatene overføres til praksis? Nei. • Annen litteratur som støtter resultatene? Ja. • **Styrke:** Følger pasientene over 5 år. • **Svakhet:** Kun 1 pasientserie, ingen gruppe til sammenligning. Pasienter rekruttert fra klinikker involvert i forskningsnettverk om familieplanlegging og reproduktivitet.

Referanse: Gemzell-Danielsson K, Schellschmidt I, Apter D: *A randomized, phase II study describing the efficiacy, bleeding profile, and safety of two low-dose levenorgestrel-releasing intrauterine contraceptive systems and Mirena.* Fertility and Sterility 2012:97;616-622	**Design: RCT** Grade: ★★(★)

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer
Å identifisere en passende dose for en ny LNG-IUS. **Konklusjon** LNG-IUS12 og LNG-IUS 16 var effektiv prevensjon som ga akseptable blødningsmønstre og var godt tolerert sammenlignet med Mirena. **Land** Finland, Sverige, Norge, Ungarn og Storbritannia. **År data innsamling** April 2005 – desember 2008	**Rekruttering deltakere:** Kvinner som ønsker prevensjon på klinikkene og via reklame. **Inkludert:** Friske parous og nulliparous kvinner, alder 21-40 år.Ultralydresultat med uteruskavitet som egner seg for str på Mirena. Regelmessig menstruasjonssyklus (21-35 d). Seksuelt aktive. **Ekskludert:** Laktasjon, vaginal fødsel, keisersnitt eller abort ≤ 12 uker før screening. Deformert uteruskavitet (f.eks. myomer). Menoragi, tidligere ektopisk graviditet, aktuell/tilbakevendende PID, kontraindikasjoner mot LNG-IUD (eks, brystkreft, kongenital uterus anomali. **Datagrunnlaget**: 742 kvinner randomisert i 3 grupper, fulgt i 3 år. LNG-IUS 12, n=239; LNG-IUS16, n: 245; Mirena, n=254. **Utfall:** Graviditet, bivirkninger relatert til progestin, blødningsmønster, plassering av IUD, endometrietykkelse, ovariestørrelse, vansker og smerter ved innsettelse, utstøting, uterusperforasjon. **Eksponeringsvariabler (validert/ikke validert)** **Viktige konfunderende faktorer** **Statistiske metoder:** SAS, Pearl index med utgangspunkt i Poisson distribusjon. Blødningsforstyrrelser etter WHO-retningslinjer.	**Graviditet:** LNG-IUS 12:1 LNG-IUS 16:5 Mirena:0 **Blødningsmønster:** Likt for alle tre typer IUD. **Ovariecyster:** LNG-IUS 12: 5,9% LNG-IUS 16: 8,6% Mirena:22,0% P < 0,0001 **Avsluttet bruk av IUD grunnet bivirkninger:** LNG-IUS 12: 15% LNG-IUS 16: 15% Mirena: 17% Vanligste: Akne, vaginalblødning, endring i humør, magesmerter og ovariecyste. **Utstøting av LNG-IUD:** LNG-IUS 12: 0,4% LNG-IUS 16: 2% Mirena: 1,6% **Fravær av dysmenore ved start og studieslutt:** LNG-IUS 12: 49,9% og 82,0% LNG-IUS 16: 49,0% og 81,0% Mirena: 43,7% og 83,7% P = 0,73 **Innsetting av IUD rapportert som "enkel" av lege:** LNG-IUS 12 & 16: 94,0% Mirena: 86,2% P < 0,001 Pas rapporterte om mindre smerter ved innsetting av LNG-IUS 12 & 16 sammenlignet med Mirena (P<0,001)	**Sjekkliste:** • **Er formålet klart formulert?** *Ja* • **Var gruppene like ved starten?** *Ikke like mtp røyking.* • **Randomiseringsprosedyre?** *Bruk av dataprogram og forseglede konvolutter.* • **Ble deltakere/studiepersonell blindet mht gruppetilhørighet?** *Kun deltagere, ikke mulig å blinde personell.* • **Ble gruppene behandlet likt utover «intervensjonen»?***Ja* • **Primære endepunktet – validert?** *Ja* • **Ble deltakernne gjort rede for på slutten av studien?** *Lost to follow-up ikke besrkevet.* • **Kan resultatene overføres til praksis?** *Ja* • **Ble alle utfallsmål vurdert?** *Ja* • **Er fordelene verdt ulemper/kostnader?** *Ja* • **Annen litteratur som styrker resultatene?** *Ja* **Hva diskuterer forfatterne som:** **-styrke:** RCT, mange deltagere **-svakhet:** Lost,to follow-up ikke beskrevet. **Har resultatene plausible forklaringer?***Ja*

Referanse: Varila E, Wahlström T, Rauramo I; *A 5-year follow-up study on the use of a levenorgestrel intrauterine system in women receiving hormone replacement therapy.* Fertility and sterility 2001;76:696-673	**Design: Kohortestudie** Grade: ★★

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer
Å undersøke endometriets histologi, blødning og effekten av å bytte LNG-IUD etter 5 års kombinert bruk med estrogen. **Konklusjon** Intrauterin levonorgestrel beskytter effektivt endometriet mot hyperplasi. Hos de fleste kvinner induserer den amenore, som kun kortvarig påvirkes av bytting av LNG-IUD. **Land** Finland **År data innsamling** Ikke beskrevet	**Inkludert:** 39 postmenopausale kvinner, fullført 12 mnd studie mtp LNG-IUD + HRT. HRT grunnet sympt. overgangsalder. **Ekskludert:** Tidligere endokarditt, malignitet,PID, infeksjon i genitalia, submucosal leiomyom, uforklarlig uterusblødning, alvorlig hirsutisme, DVT. 29 kvinner fikk tilbud om å fortsette HRT +LNG-IUD.. **Behandlingsfri 3 mnd før ny LNG-IUD**: n = 7 **Umiddelbar ny LNG-IUD**: n = 22 3 mnd uten behandling etter fjerning av 1. → vurdere endometriets tilheling **Intervensjon:** Endometrieprøver til histolog, vurdering av endometrietykkelse, UL ved fjerning LNG-IUD, blødningsdagbok ført av pas. **Utfall – hoved utfall:** Endometriets histologi og tykkelse, effekter av østrogen og progestin. Blødningsmønster via «blødningsdagbøker». Vurdering av insetting, fjerning og reinnsetting LNG-IUD av pas og lege. **Histopat. Endometriet:** Østrogen stim: 0 = atrofisk endometrium, 1 = lite stim av atrofisk endometrium, 2= sterkere østrogenstim., 3 = slutten av normal proliferativ fase i syklus. Progestineffekt vurdert med normsl syklus som ref. på samme måte. **Statistiske metoder:** Resultater angitt i prosent, gjennomsnitt med standardavvik eller median med omfang.	**Hovedfunn (etter 5 års bruk)** <u>Tykkelse endometriet:</u> median 2,4 mm. <u>Histopatologi endometriet:</u> Progestogen-stimuli av endometriet vurdert som moderat (2) og sterk (3) i 28 av 29 biopsier. Ingen prøver med endometriehyperplasi. Østrogenstim vas synlig i alle prøver, med skår mellom 1 og 2 → suppresjon av endometriet. **Innsetting (1. og 2.):** Ingen smerter: 19 og 18 Milde smerter: 13 og 10 Moderate smertert: 7 og 0 Sterke smerter: 1 og 1 Innsetting enkel: 26 og 14 Innsetting vanskelig: 27 og 2 **Blødning:** 35 av 39 kvinner rapporterte ingen blødningsdager. 10 kvinner rapporterte småblødninger det 1. året. 25 kvinner med amenore. Kvinner med behandlingsfri 3 mnd rapporterte om småblødninger (ikke mer enn 11 dager) i perioden uten behandling. Median blødningsdager = 0 tre mnd etter ny innsetting hos begge grupper.	**Sjekkliste:** • **Er formålet klart formulert?**Ja • **Var studien basert på et tilfeldig utvalg fra en egnet pasientgruppe?** Usikkert • **Var inklusjonskriteriene klart definert?** Ja • **Var alle pasientene i samme stadium av sykdommen?** Ja • **Var responseraten høy nok?** Ja • **Ble det brukt objektive kriterier for å vurdere/validere endepunktene?** Ja • **Ved sammenligninger av pasientserier, er seriene tilstrekkelig beskrevet?** Nei • **Er prognostiske/konfunderende faktorer beskrevet/tatt hensyn til i design/anal?**Ja • **Var registreringen prospektiv?**Ja • **Var oppfølgningen lang nok!**Ja • **Var oppfølgningen tilstrekkelig for å nå endepunktene?** Ja • **Kan resultatene overføres til praksis?** Liten pasientgruppe. • **Annen litteratur som støtter resultatene?**Ja **Hva diskuterer forfatterne som:** • **Styrke:** Lang nok oppfølging, alle endepunktene vurdert. • **Svakheter:** Lite pasientgrunnlag, ulik størrelse på gruppene. **Har resultatene plausible biologiske forklaringer?** Ja