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A nationwide drug utilization study

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Published in:
Contraception

DOI (link to publication from Publisher):
[10.1016/j.contraception.2019.12.013](https://doi.org/10.1016/j.contraception.2019.12.013)

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Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Meaidi, A., Kuhr Skals, R., Alexander Gerds, T., Lidegaard, O., & Torp-Pedersen, C. (2020). Decline in Danish use of oral tranexamic acid with increasing use of the levonorgestrel-releasing intrauterine system: A nationwide drug utilization study. *Contraception*, *101*(5), 321-326. <https://doi.org/10.1016/j.contraception.2019.12.013>

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Original Research Article

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PII: S0010-7824(19)30504-9
DOI: <https://doi.org/10.1016/j.contraception.2019.12.013>
Reference: CON 9376

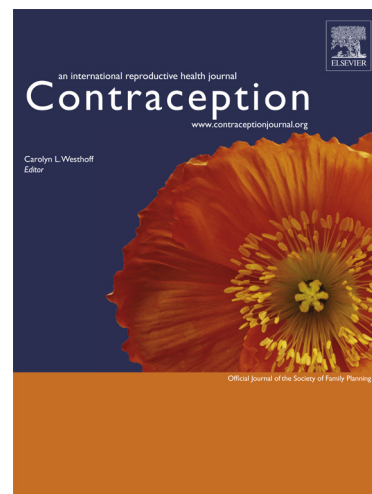
To appear in: *Contraception*

Received Date: 16 July 2019
Revised Date: 8 December 2019
Accepted Date: 11 December 2019

Please cite this article as: A. Meaidi, R. Kuhr Skals, T. Alexander Gerds, O. Lidegaard, C. Torp-Pedersen, Decline in Danish use of oral tranexamic acid with increasing use of the levonorgestrel-releasing intrauterine system, A nationwide drug utilization study, *Contraception* (2019), doi: <https://doi.org/10.1016/j.contraception.2019.12.013>

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**Decline in Danish use of oral tranexamic acid with increasing use of the
levonorgestrel-releasing intrauterine system,
A nationwide drug utilization study**

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Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. CTP declares grants from Bayer outside the current research, and OL declares receiving honoraria for speeches in pharmacoepidemiological issues outside the current research. AM, RS, and TG report no conflicts of interest.

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Word count; Abstract:306, Main text:

Abstract

Objective: To study patterns of oral tranexamic acid use among pre- and perimenopausal Danish women following the introduction of the levonorgestrel-releasing intrauterine system.

Study design: We conducted a nationwide descriptive drug utilization study including all 15-54-year-old Danish women during the period 1996-2017. National health registers provided information on use of oral tranexamic acid, the levonorgestrel-releasing intrauterine system, other hormonal contraceptives, and cyclical oral progestogens as well as incidence rates of endometrial ablations and hysterectomies. Linear calendar time trends in usage of these treatments were tested using Poisson and logistic regression models, which adjusted for user age and provided p-values for significance.

Results: During the study period, use of the levonorgestrel-releasing intrauterine system increased 14-fold among women aged 15-54 years, from 2.3 in 1996 to 32 users per 1,000 person-years in 2017 ($p < 0.001$). The increase happened consistently throughout the study period for women aged 20-54 years, but not for the youngest age group, 15-19 years, among whom the increase only happened in the end of study period following the introduction of a levonorgestrel-releasing intrauterine system with a smaller frame.

Use of oral tranexamic acid declined from 11.3 in 1996 to 6.3 per 1,000 person-years in 2017 among women aged 20-54 years ($p < 0.001$) but increased from 1.4 to 1.9 users per 1,000 person-years among those aged 15-19 years ($p < 0.001$).

Use of other hormonal contraceptives remained stable over time at around 300 users per 1,000 person-years, while the use of cyclical oral progestogens decreased from 4 to 0.1 users per 1,000 person-years ($p < 0.001$). The incidence of hysterectomies decreased from 3.1 to 2.1 per 1,000 person-years ($p < 0.001$), while the incidence rate of endometrial ablations increased from 0.7 to 1.3 per 1,000 person-years ($p < 0.001$).

Conclusions: In Denmark, increasing use of the levonorgestrel-releasing intrauterine system has been accompanied by a decrease in use of oral tranexamic acid, cyclical oral progestogens, and hysterectomy.

Keywords: Endometrial ablation, heavy menstrual bleeding, hormonal contraception, hysterectomy, levonorgestrel-releasing intrauterine system, tranexamic acid

Implication

Increasing use of the levonorgestrel-releasing intrauterine system was accompanied by declining use of other therapies used to decrease menstrual bleeding. The non-contraceptive benefits of hormonal contraception should be considered in cost-effectiveness analyses.

Journal Pre-proofs

1. Introduction

Hormonal contraceptive methods are recognized as effective treatment options for heavy menstrual bleeding.[1 2 3] Containing progestins/progesterone, hormonal contraceptives inhibit normal proliferative changes in the endometrium, causing endometrial atrophy and thereby reduction in menstrual blood loss.[4] Compared to combined oral contraceptives, the levonorgestrel-releasing intrauterine system has shown to be associated with a greater reduction in heavy menstrual bleeding and a larger improvement of quality of life.[2]

The levonorgestrel-releasing intrauterine system has also shown to be superior in the treatment of heavy menstrual bleeding compared to other non-contraceptive medical therapies, such as oral tranexamic acid. [2] Tranexamic acid is an anti-fibrinolytic agent given to people experiencing heavy bleeding. By reversibly binding to plasminogen, tranexamic acid prevents the binding and lysis of fibrin, thereby preserving fibrin's haemostatic structure. [5] Since the release of tranexamic acid in the 1960s, the orally administrated version of the drug has been prescribed to women with heavy menstrual bleeding. [6 7]

In Denmark, oral tranexamic acid is mostly used by women of reproductive age, with heavy menstrual bleeding as the main indication for this treatment. [8] Thus, changes in patterns of oral tranexamic acid utilization among Danish women could potentially have occurred following the introduction of the levonorgestrel-releasing intrauterine system to the Danish market in the year 1990. Furthermore, in 2013, a smaller sized levonorgestrel-releasing intrauterine system was introduced to the market, also potentially changing use of oral tranexamic acid.

We aimed to describe the use of oral tranexamic acid among Danish women aged 15-54 years following the introduction of the levonorgestrel-releasing intrauterine system in Denmark. To further explore the link between the use of these two drugs, we also assessed use of other medical and surgical therapies for heavy menstrual bleeding.

2. Material and methods

2.1 Study population

Using information on birth, migration, and death provided by The Danish Civil Registration System and The National Danish Register of Causes of Death, we identified all person-years contributed by 15-54-year-old women alive and living in Denmark during the period 1996-2017. [9 10]

2.2 Outcomes of interest

In Denmark, all redeemed prescriptions are registered in the Danish National Register of Medicinal Product Statistics (“prescription register”). [11] The register holds information on expedition date, number of purchased packages, size of each package, as well as type and size of the drug unit of all redeemed prescription since the year 1995. [11]

2.2.1 The levonorgestrel-releasing intrauterine system

Information on exposure to the levonorgestrel-releasing intrauterine system in the study population was provided by searching the Anatomical Therapeutic Chemical code of the levonorgestrel-releasing intrauterine system (ATC code G02BA03) in the prescription register.[11] Use of levonorgestrel-releasing intrauterine system was assessed as user rates according to five-year age groups and/or calendar time.

User rates of the levonorgestrel-releasing intrauterine system were calculated as number of women who redeemed at least one prescription of the levonorgestrel-releasing intrauterine system in a given calendar year and/or age group and reported per 1,000 person-years.

2.2.2 Oral tranexamic acid

Information on exposure to oral tranexamic acid in the study population was also provided by the prescription register (ATC code B02AA02), the assessment restricted to tablets only. Use of oral tranexamic acid was assessed according to five-year age groups and/or calendar time. The assessment included user rates as well as total and median number of prescriptions and dose redeemed.

User rates of oral tranexamic acid were calculated as number of women who redeemed at least one prescription of oral tranexamic acid in a given calendar year and/or age group and reported per 1,000 person-years. A sub-assessment of annual user rates was made for only first-time users, defined as women who, prior to the year in which they were included as users, did not redeem any prescription of oral tranexamic acid.

Doses were reported in grams. From April 2004, a dosage variable was added to the prescription register, making it possible to extract information on dosage regimen prescribed. [11] However, due to inconsistent reporting, dosage information was only available for 67 % of redeemed prescriptions of oral tranexamic acid, 80 % of these with a dosage regimen of 1 gram x 3 daily for five days. Thus, 15 grams of oral tranexamic acid was considered to cover the treatment of one menstrual cycle.

2.2.3 Other treatments for heavy menstrual bleeding

The prescription register also provided information on use of other hormonal contraceptives (G03AA, G03AB, G03AC, G02BB01, G03HB01), cyclical oral progestogens (G03DA02, G03DB08), and ulipristal acetate (G03XB02). We excluded use of cyclical oral progestogens, if it was used as hormonal therapy/hormonal replacement therapy (G03C, G03F).

By searching relevant procedural codes (codes of the Nordic Medico-Statistical Committee Classification of Surgical Procedures) in The Danish National Patient Register, we achieved information on endometrial ablation (KLCA16, KLCB28, KLCB32), hysterectomy (KLCC10, KLCC11, KLCC20, KLCD), myomectomy (KLCB10, KLCB11, KLCB20), and uterine fibroid embolization (KPDT40), experienced by the study population. [12]

Use of these drugs and surgical procedures was assessed according to calendar time and five-year age groups. The assessment included user rates, which were calculated as number of women who redeemed at least one prescription of the respective drugs/experienced the respective surgical procedures in a given calendar year and age group and reported per 1,000 person-years.

Furthermore, among oral-tranexamic acid users, we calculated the proportion of women, who became users of these other therapies or the levonorgestrel-releasing intrauterine system within twelve months from first prescription of oral tranexamic acid.

2.3 Statistical analyses

Linear calendar time trends in user rates were tested using Poisson regression, while linear calendar time trends in binary outcomes of interest were tested using logistic regression. The regression models included an age group variable to test if the linear calendar time trends were independent of the annual distribution of age in the study population. The level of statistical significance was set at 5%. Data were analysed using SAS, version 9.4 (SAS Institute).

2.4 Ethics Approval

The study was approved by the Danish Data Protection Agency and the Danish Health Data Board. Ethics approval from the Danish National Committee on Health Research Ethics is not required for register-based studies.

3. Results

3.1 Use of the levonorgestrel-releasing intrauterine system and oral tranexamic acid by the study population

During the 22-year-long study period, 278,334 Danish women aged 15-54 years bought 368,849 levonorgestrel-releasing intrauterine systems.

The annual user rate of levonorgestrel-releasing intrauterine system increased 14-fold during the study period, from 2.3 to 32 users per 1,000 person-years ($p < 0.001$, figure 1). Use of the levonorgestrel-releasing intrauterine system increased consistently in all age groups, except in the youngest age group (15-19-year-olds), where the increase happened abruptly after the year 2013 (figure 2). Throughout the entire study period, usage peaked among women aged 35-44 years and was lowest among the youngest (15-19 years) and oldest (50-54 years) age group.

Oral tranexamic acid was used by 152,878 15-54-year-old Danish women, who redeemed a total of 388,969 prescriptions from 1996 to 2017. In all years studied, the median of redeemed oral tranexamic acid was 1 prescription of 15 grams, accounting for the treatment of one menstrual cycle. Use according to five-year age groups are shown in supplementary table 1. During the study period, Danish hospitals used 14.9 % of oral tranexamic acid for inpatients. This tranexamic acid was not included in this study due to it not being registered on an individual level in the prescription register. [8]

Among the entire study population, the annual user rate of oral tranexamic acid declined throughout the study period from 10.1 to 5.7 users per 1,000 person-years (43.6 % decline, $p < 0.001$, figure 1). A sub-assessment of only first-time users showed a similar decline by time ($p < 0.001$, supplementary figure 1). Figure 3 illustrates time trends according to five-year age groups. For all included age groups above the age of 19, the annual user rate of oral tranexamic acid decreased by time ($p = 0.024$ for age group 20-24 years; $p < 0.001$ for the rest). The decline in annual users from 1996 to 2017 ranged from 23.6 % in women aged 20-24 years to 50.0 % in 35-44-year-old women. In 15-19-year-old women, however, the annual user rate increased by 40.1 % from 1996 to 2017 ($p < 0.001$).

Figure 4 illustrates the almost linear correlation between annual user rate of oral tranexamic acid and the annual user rate of the levonorgestrel-releasing intrauterine system, the slope of the correlation suggesting a decline of one user of oral tranexamic acid for every 6.5 additional users of the levonorgestrel-releasing intrauterine system.

3.2 Use of other treatments for heavy menstrual bleeding among the study population

No time trend was observed for the use of other hormonal contraceptives (annual user rate of around 300 users per 1,000 person-years).

The annual user rate of cyclical oral progestogens declined from 4 in 1996 to 0.1 users per 1,000 person-years in 2017 ($p<0.001$).

The annual incidence rate of endometrial ablations increased from 0.7 to 1.3 per 1,000 person-years ($p<0.001$), while the incidence rate of hysterectomies decreased throughout the study period from 3.1 to 2.1 hysterectomies per 1,000 person-years ($p<0.001$).

Supplementary figure 2-5 show the time trends according to five-year age groups.

Time trends in use of uterine fibroid-specific treatments are shown in supplementary figure 6. These treatments were rarely used throughout the study period, the average annual incidence rate being 0.24 per 1,000 person-years.

3.3 Treatments among users of oral tranexamic acid

Of the 152,878 women redeeming at least one prescription of oral tranexamic acid during 1996-2017, 148,027 (97 %) could be followed for one year from first prescription of oral tranexamic acid (all women included, except those being first-time users in 2017). Of these, only 54,717 (40.0%) either redeemed a prescription of the levonorgestrel-releasing intrauterine system, another hormonal contraceptive, or cyclical oral progestogens or experienced an endometrial ablation or hysterectomy within the first year after their first redemption of an oral tranexamic acid prescription. The proportion of women receiving one of these treatments within a year from their first prescription of oral tranexamic acid increased from 29.9 % in 1996 to 40.9 % in 2016 ($p<0.001$). Table 1 shows use of these treatment options within twelve months after first prescription of oral tranexamic acid according to calendar time. Use of the levonorgestrel-releasing intrauterine system within twelve months from first usage of oral tranexamic acid increased significantly over time ($p<0.001$). Same did the proportion of women getting an endometrial ablation ($p<0.001$). Use of cyclical oral progestogens declined over time ($p<0.001$), while use of other hormonal contraceptives and hysterectomies did not change considerably or systematically throughout the period. Treatments received within a year from first prescription of oral tranexamic acid are shown according to five-year age groups in supplementary table 2. Use of the levonorgestrel-releasing intrauterine system peaked in the 35-49-year-olds, whereas use of other hormonal contraceptives within a year from oral tranexamic acid usage peaked in the youngest age group.

4. Discussion

This nationwide study shows as use of the levonorgestrel-releasing intrauterine system increased 14-fold among Danish women aged 15-54 years over the past two decades, a clinically and statistically significant decline occurred in use of oral tranexamic acid among the 20-54-year-olds. In addition, rate of hysterectomies decreased throughout the study period, confirming prior reports on the ability of the levonorgestrel-releasing intrauterine system to significantly reduce menstrual blood loss. [2]

The levonorgestrel-releasing intrauterine system is known to both effectively treat heavy menstrual bleeding and to reduce the risk of development of heavy menstrual bleeding in women using it for contraceptive purposes. [2] Furthermore, the levonorgestrel-releasing intrauterine system has shown to be superior in reducing heavy menstrual bleeding and in reducing the effect of heavy menstrual bleeding on quality of life compared to other medical therapies, including oral tranexamic acid. [2, 13] Thus, the 14-fold increase in use of the levonorgestrel-releasing intrauterine system observed throughout the study period could explain the observed decline of both repeat-users and first-time-users of oral tranexamic acid, although we recognize that other factors may have influenced the change in oral tranexamic acid utilization.

In this study, use of the levonorgestrel-releasing intrauterine system among 15-19-year-olds did not increase significantly until after 2013, when a smaller intrauterine system was introduced to the Danish market for nulliparous. Although increasing, the user rate of the levonorgestrel-releasing intrauterine system in the age group 15-19 years was the lowest of all age groups. We interpret these findings as indications of hesitance of using the intrauterine system in young females, and we believe that this hesitance could explain, why we do not see a decline in oral tranexamic acid usage among females aged 15-19 years.

Acknowledgement/Funding

This work was supported by The Danish Heart Foundation [16-R107-A6715-22964] and The Department of Gynaecology, Rigshospitalet.

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Tables

Table 1:

Treatments for heavy menstrual bleeding within twelve months after first prescription of oral tranexamic acid by year

Age group	First-time users of oral tranexamic acid (n)	Levonorgestrel-releasing intrauterine system	Other hormonal contraceptives	(% of n)		
				Cyclical oral progestogens	Endometrial ablation	Hysterectomy
1996	13,976	2.6	15.4	4.5	2.3	7.2
1997	10,046	2.4	16.7	4.7	3.1	6.6
1998	8,911	2.9	16.8	4.5	3.1	6.6
1999	8,545	3.5	18.5	4.1	2.8	6.6
2000	7,335	4.6	18.1	3.8	3.4	6.9
2001	7,360	5.6	19.0	3.8	3.0	7.1
2002	7,709	5.9	20.9	3.9	3.4	6.9
2003	7,190	6.1	20.1	3.6	4.1	6.9
2004	7,178	6.9	20.8	4.0	4.4	6.6
2005	6,711	8.0	21.2	3.3	4.6	6.0
2006	6,685	8.4	21.8	3.3	4.6	6.5
2007	6,581	8.9	20.6	3.1	4.4	6.2
2008	6,204	9.6	21.3	2.6	4.8	6.7
2009	6,092	9.7	21.9	2.1	5.3	7.1
2010	5,952	10.3	22.7	2.2	5.2	6.7
2011	5,790	10.4	22.8	1.9	5.4	6.7
2012	5,519	11.0	21.6	1.8	6.1	6.5
2013	5,470	10.8	20.3	1.4	6.1	6.9
2014	4,962	10.1	20.1	0.9	6.7	7.0
2015	4,830	11.7	20.1	0.6	6.3	6.1
2016	4,981	11.8	20.5	0.4	6.4	6.6
Total	148,027	6.9	19.6	3.2	4.3	6.7

Figure Legends

Figure 1:

Rates of the levonorgestrel-releasing intrauterine system, oral tranexamic acid, and cyclical oral progestogens as well as incidence rates of hysterectomies and endometrial ablations among women aged 15-54 years during the period 1996-2017.*

* calculated as number of women who redeemed at least one prescription of the respective drugs in a given calendar year per 1,000 person-years.

Annual rate of other hormonal contraceptives was rather stable throughout the study period, around 300 per 1,000 person-years.

Figure 2:

Rates of the levonorgestrel-releasing intrauterine system according to five-year age groups during the period 1996-2017.*

* calculated as number of women who redeemed at least one prescription of the levonorgestrel-releasing intrauterine system in a given calendar year and age group per 1,000 person-years.

Figure 3:

Rates of oral tranexamic acid according to five-year age groups during the period 1996-2017.*

* calculated as number of women who redeemed at least one prescription of oral tranexamic acid in a given calendar year and age group per 1,000 person-years.

Figure 4:

Correlation between annual rates of oral tranexamic acid and the levonorgestrel-releasing intrauterine system among 15-54-year-old women during the period 1996-2017.*

*calculated as number of women who redeemed at least one prescription of the respective drugs in a given calendar year per 1,000 person-years.

Supplementary Material

Supplementary table 1:

Use of oral tranexamic acid according to five-year age groups among 15-54-year-old Danish women during the period 1996-2017.

Age group	Users		First-time users		Prescriptions			Dose		
	n	%	n	% of users	n	%	n per user*	gram	%	gram per user*
15-19	4,729	2.6	-	-	8,512	2.0	1 (1-2)	186,481	2.1	15 (15-30)
20-24	7,332	4.0	6,762	92.2	10,702	2.6	1 (1-1)	220,763	2.5	15 (15-30)
25-29	11,418	6.2	10,408	91.2	16,964	4.2	1 (1-1)	327,654	3.7	15 (15-30)
30-34	17,266	9.4	15,350	88.9	29,670	7.6	1 (1-2)	584,841	7.1	15 (15-30)
35-39	24,894	13.5	21,278	85.5	50,359	13.1	1 (1-2)	1,040,816	12.7	15 (15-30)
40-44	36,606	19.9	30,626	83.7	81,946	21.4	1 (1-2)	1,753,585	21.5	15 (15-45)
45-49	48,462	26.3	39,252	81.0	114,677	29.7	1 (1-2)	2,499,928	30.3	30 (15-45)
50-54	33,283	18.1	24,473	73.5	76,139	19.4	1 (1-2)	1,671,866	20.0	30 (15-45)
Total	183,990	100.0	152,878	83.1	388,969	100.0	1 (1-2)	8,285,934	100.0	15 (15-45)

*Median (1st quantile - 3rd quantile)

Supplementary table 2:

Treatments for heavy menstrual bleeding within twelve months after first prescription of oral tranexamic acid by five-year age groups

Age group	First-time users of oral tranexamic acid (n)	Levonorgestrel-releasing intrauterine system	Other hormonal contraceptives	Cyclical oral progestogens	Endometrial ablation	Hysterectomy
(% of n)						
15-19	4,488	2.0	68.1	0.2	0.0	0.0
20-24	6,445	3.0	58.8	0.5	0.1	0.1
25-29	9,990	3.7	44.9	0.7	0.3	0.7
30-34	14,891	6.0	31.9	0.9	1.5	2.4
35-39	20,682	8.1	21.5	1.8	3.9	5.4
40-44	29,821	9.2	13.8	3.2	6.5	9.3
45-49	38,101	8.3	8.6	5.1	6.2	6.7
50-54	23,609	4.7	4.7	5.1	4.3	8.2
Total	148,027	6.9	19.6	3.2	4.3	6.7

Supplementary figure 1:

Rates of oral tranexamic acid according to prior experience with oral tranexamic acid during the period 1996-2017.*

*calculated as number of women who redeemed at least one prescription of oral tranexamic acid in a given calendar year per 1,000 person-years. A woman was defined as a first-time user at time of her first redemption of a prescription of oral-tranexamic acid.

Supplementary figure 2:

Rates of other hormonal contraceptives according to five-year age groups during the period 1996-2017.*

*calculated as number of women who redeemed at least one prescription of a hormonal contraceptive other than the levonorgestrel-releasing intrauterine system in a given calendar year and age group per 1,000 person-years.

Supplementary figure 3:

Rates of cyclical oral progestogens according to five-year age groups during the period 1996-2017.*

*calculated as number of women who redeemed at least one prescription of cyclical oral progestogens (without prior or simultaneous redemption of estrogens) in a given calendar year and age group per 1,000 person-years.

Supplementary figure 4:

The annual incidence rate of women having an endometrial ablation according to five-year age groups during the period 1996-2017.

Supplementary figure 5:

The incidence rate of women having a hysterectomy according to five-year age groups during the period 1996-2017.

Supplementary figure 6:

The annual incidence rate of a) women having a myomectomy, b) uterine fibroid embolization, and the annual rate of c) ulipristal acetate in women aged 15-54 years during the period 1996-2017.*

*calculated as number of women who redeemed at least one prescription of ulipristal

