

# Method of Hormonal Contraception and Protective Effects Against Ectopic Pregnancy

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**OBJECTIVE:** To estimate the incidence rates for ectopic pregnancy by contraceptive method in a cohort of women using hormonal contraception in Sweden between 2005 and 2016.

**METHOD:** Women aged 15–49 years with a filled prescription for a hormonal contraceptive in the Swedish Prescribed Drug Register between 2005 and 2016 were included. For each woman, all exposed woman-years were allocated to treatment episodes depending on the method of contraception. Treatment time started on the day the prescription was filled and ended on the first day of the end of supply, new eligible dispensing, pregnancy-related diagnosis and its associated estimated last menstrual period, or removal procedure. *Ectopic pregnancy* was

defined as having at least two records of International Classification of Diseases, Tenth Revision code O00-, including O00.0, O00.1, O00.2, O00.8, O00.9, within 30 days or one episode of O00- and one surgical procedure for ectopic pregnancy (NOMESCO Classification of Surgical Procedures code LBA, LBC, LBD, LBE, LBW). Incidence rates per 1,000 woman-years and 95% CIs were calculated for each method of contraception.

**RESULTS:** The study included 1,663,242 women and 1,915 events of ectopic pregnancy. The incidence rate (95% CI) for ectopic pregnancy per method of hormonal contraception was estimated: 13.5-mg levonorgestrel (LNG) hormonal intrauterine device (IUD), 2.76 (2.26–3.35) per 1,000 woman-years; 52-mg LNG hormonal IUD, 0.30 (0.28–0.33) per 1,000 woman-years; combined oral contraception, 0.20 (0.19–0.22) per 1,000 woman-years; progestogen implants, 0.31 (0.26–0.37) per 1,000 woman-years; oral medium-dose progestogen (desogestrel 75 mg), 0.24 per 1,000 woman-years, (0.21–0.27); and oral low-dose progestogen (norethisterone 0.35 mg and lynestrenol 0.5 mg), 0.81 (0.70–0.93) per 1,000 woman-years.

**CONCLUSION:** Hormonal contraception lowers the risk of ectopic pregnancy markedly. The incidence rate of ectopic pregnancy among women using a low-dose hormonal IUD (13.5 mg LNG) was substantially higher than that in women using other types of hormonal contraception. This study provides real-world evidence to inform best clinical practice for women-centered contraceptive counseling. (*Obstet Gynecol* 2022;139:764–70)

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Ectopic pregnancy is a major cause of maternal morbidity and mortality globally, accounting for approximately 4% of the maternal mortality in the United Kingdom.<sup>1</sup> Ectopic pregnancy also causes significant morbidity in the form of surgical procedures, medication with methotrexate, and reduced fertility, which may result in subsequent need for assisted reproductive technology.<sup>2–4</sup> Approximately 2% of all pregnancies are ectopic.<sup>5</sup> In Sweden, where the current study took place,

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the average incidence rate of ectopic pregnancy from 2008 to 2016 was approximately 0.83 cases per 1,000 woman-years for ages 15–49 years.<sup>6</sup> The incidence has increased in the past decade, and contraception failure has been discussed as one plausible factor contributing to the increase.<sup>7</sup> In 2019, 49% of all women of reproductive age (15–49 years) worldwide were using some form of contraception.<sup>8</sup>

It is estimated that approximately 450 million women use hormonal or intrauterine contraception daily worldwide.<sup>9</sup> Hormonal contraception may be either a combination of estrogen and a progestogen (pills, patches, or vaginal rings) or progestogen only (pills, intrauterine devices [IUDs], implants, or injections). The most effective protection from experiencing an ectopic pregnancy is to use a modern contraceptive method and, thereby, reduce risk of unintended pregnancy. Long-acting reversible contraception, including hormonal IUDs, are user independent with a low risk of unintended pregnancy and, in Sweden, are often favored by young nulliparous women.<sup>10–13</sup> However, if pregnancy occurs, approximately 25–50% of these pregnancies are ectopic pregnancies.<sup>14</sup> The risk of ectopic pregnancy with use of other hormonal contraception is less studied.<sup>13,15–17</sup> There are studies indicating that progestogen-only hormonal contraception is associated with an increased risk of ectopic pregnancy.<sup>16</sup> Currently, there are three types of hormonal IUDs available on the European market (including Sweden), containing 13.5, 19.5, and 52 mg of levonorgestrel (LNG). The hormonal IUD with 13.5 mg LNG with a smaller insertion tube was introduced in Sweden in 2014. After its introduction, use of hormonal IUDs in nulliparous women increased significantly. The hormonal IUD with the lowest dose has been reported in a small study (N=1,040 women) to be associated with a higher risk of ectopic pregnancy when compared with the 52-mg LNG hormonal IUD.<sup>18</sup> In 2017, new text about the risk of ectopic pregnancy was included in the summary of products characteristics.

The aim of this population-based national register study was to estimate the incidence rate for ectopic pregnancy by contraceptive method in a cohort of women aged 15–49 years using hormonal contraception in Sweden between 2005 and 2016.

## METHODS

Sweden has population-based national registers, which include information for all inhabitants on demographic and health indicators such as births, dispensed drugs, and hospital contacts. The popula-

tion of Sweden is approximately 10 million, and the Swedish government has given consent for each individual's data to be included. All registers include the civil registration number of each resident, a unique number assigned at birth or immigration that allows linkage of individual data between registers.<sup>19,20</sup> We obtained linked data from three national registers: the Prescribed Drug Register, the National Patient Register, and the Medical Birth Register. The Medical Birth Register includes maternal data such as parity, the date of the last menstrual period, and pregnancy outcomes including date of birth of the neonate. The Prescribed Drug Register includes data on dispensed substances, dispensed dose, package sizes, and formulations according to the Anatomical Therapeutic Chemical (ATC) Classification System, including the date of dispensation, from July 1, 2005.<sup>20</sup> The National Patient Register includes all in-patient admissions and outpatients visits to the Swedish hospitals, and their associated diagnosis according to the International Classification of Diseases, Tenth Revision (ICD-10) codes.

In a Swedish setting, most women receive contraceptive counseling by midwives at booked appointments or during drop-in visits at maternity health clinics. Most contraceptive counseling and prescription is performed by midwives within the public health system and free of charge. All medication, including hormonal contraception, is free of charge for women aged 18 years or younger. For women up to 26 years of age, contraception is subsidized. Hormonal contraception requires a prescription. Removal of long-acting reversible contraceptives is performed free of charge by a midwife at patient request. Women who choose to have contraceptive counseling, prescription, insertion, or removal performed by a medical doctor pay a fee for the visit.

In Sweden, all suspected cases of ectopic pregnancy are routinely referred by any health care professional to hospital care because of the need for rapid follow-up, repeated serum human chorionic gonadotropin testing, and assessment for surgical or medical (methotrexate) treatment.

All women in Sweden registered in the Prescribed Drug Register with a filled prescription of a hormonal contraceptive (ATC code G02B or G03A), excluding spermicides (ATC code G02BB) and emergency contraceptive pills (ATC code G03AD01 or G03AD02), between July 1, 2005, and December 31, 2016, were included in the study population. Eligible dates were all dates with filled prescriptions of a unique ATC code, excluding dates with filling of two or more different contraceptives. The date of the

first filled eligible prescription during the study period was defined as the index date. Women older than age 50 years and women who had undergone a sterilization procedure before the index date were excluded from the source population. All women were followed from the index date until their 50<sup>th</sup> birthday, sterilization, death, emigration, or the administrative end of the study data linkage (December 31, 2016).

For each woman, all exposed woman-years were allocated to treatment episodes, depending on the method of contraception: hormonal IUDs containing 13.5 mg (ATC code G02BA) or 52 mg LNG (ATC code G02BA), combined hormonal contraceptives (patches ATC code G03AA13, vaginal rings ATC code G02BB0, and pills ATC codes G03AA and G03AB), etonogestrel implants (ATC code G03AC08), oral medium-dose progestogen-only (desogestrel 75 mg, ATC code G03AC09), oral low-dose progestogen-only (norethisterone 0.35 mg and lynestrenol 0.5 mg, ATC code G03AC01-02), and medroxyprogesterone acetate injections (ATC code G03AC06). Unexposed time was not included.

The length of treatment time started at dispensing date and ended on the first day of end of supply, new eligible dispensing, pregnancy related diagnosis and its associated estimated last menstrual period, or removal procedure (for IUDs or implants). Individual dispensings were summed into treatment episodes by adding the treatment time for each dispensing with a maximum gap of seven days (grace period) between stop of the current dispensing and start of next dispensing of the same contraceptive agent. Women could reenter the cohort with a new dispensing of a prescription.

*Ectopic pregnancy* was defined as at least two records of ectopic pregnancy (ICD-10 code O00-, including O00.0, O00.1, O00.2, O00.8, O00.9) within 30 days or one record of ectopic pregnancy and a procedure code for surgery for ectopic pregnancy (NOMESCO Classification of Surgical Procedures code LBA, LBC, LBD, LBE, LBW) during the same treatment episode. Within the 30-day window, the first fulfilled definition of ectopic pregnancy was used as the date for the outcome.

The survival curves were adjusted for the identified available confounders age (younger than 40 years, 40 years or older), diagnosis of endometriosis (ICD-10 code N80, yes or no), and previous ectopic pregnancy (defined as above, yes or no).

Baseline characteristics of the study population were expressed as numbers and proportions. The number of events (ectopic pregnancies) and woman-years for each contraceptive method and risk factor

were tabulated. Incidence rates by contraceptive method and by risk factor were calculated with 95% confidence limits using Byar's method. A sensitivity analysis excluding treatment episodes with a history of ectopic pregnancy was performed.

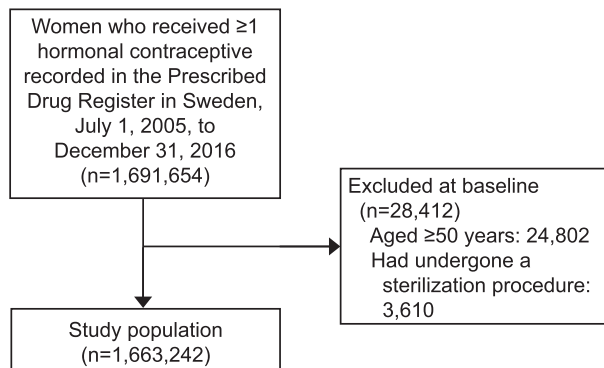
A Cox regression model adjusted for age, history of endometriosis, previous ectopic pregnancy, and contraceptive class was fitted to time to ectopic pregnancy, assuming proportional hazards between levels within each covariate. The analytic unit was treatment episodes, allowing each woman to contribute more than once and to more than one contraceptive method. The fitted model was used for prediction (as opposed to those observed directly in the data) of survival probabilities and was presented as graphs of 1-P compared with survival time in years for each specific combination of age, history of endometriosis, and previous ectopic pregnancy covering the 13.5-mg LNG hormonal IUD and the three most common hormonal contraceptive methods (52-mg LNG hormonal IUD, combined oral contraception, and oral medium-dose progestogen-only contraception). Ethical permission for the study was granted by the regional ethical committee in Stockholm (diary number 2014/1884-31).

## RESULTS

The study population included a total of 1,663,242 women who contributed a total of 6,807,293 treatment episodes, which totalled 6,960,110 woman-years. Figure 1 describes the study population flow chart. The study participants had a mean age of 27 years, and the majority (64%) were nulliparous at the inclusion in the cohort. Table 1 describes the baseline characteristics of the participants at the index date. Combined oral contraception contributed the most woman-years (40.1%) in the cohort, followed by the 52-mg LNG hormonal IUD (24.7%). Table 2 shows the total prescriptions and associated number of woman-years per contraceptive method.

There were 1,915 ectopic pregnancies during the study period resulting in an incidence rate of 0.28 per 1,000 woman-years (95% CI 0.26–0.29). Among women with a history of endometriosis, the incidence rate was 0.25 (95% CI 0.12–0.44) per 1,000 woman-years and was 6.09 (95% CI 4.88–7.50) per 1,000 woman-years for women with a history of ectopic pregnancies. No woman in the study had both a history of previous ectopic pregnancy and endometriosis at time of inclusion in the cohort.

The 13.5-mg LNG hormonal IUD was used by 2.3% of the study population, of whom 104 had an ectopic pregnancy (incidence rate 2.76 per 1,000



**Fig. 1.** Population flow chart.

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woman-years, 95% CI 2.26–3.35). The hormonal 52-mg LNG IUD was used by 26.1% of the study population, of whom 522 had an ectopic pregnancy (incidence rate 0.30 per 1,000 woman-year, 95% CI 0.28–0.33). Table 2 and Figure 2 describe the incidence

**Table 1. Baseline Characteristics of Women in the Study Population at the Time of the First Contraceptive Dispensing, July 1, 2005–December 31, 2016 (N=1,663,242)**

Characteristic	Value
Age (y)	27.0±9.9
Younger than 15	59,368 (3.6)
15–19	513,146 (30.9)
20–29	481,773 (29.0)
30–39	376,020 (22.6)
40–50	232,935 (14.0)
Highest level of education	
Elementary school	402,134 (24.2)
High school	544,385 (32.7)
College or university	418,262 (25.2)
Postgraduate	5,257 (0.3)
Missing	293,204 (17.6)
Parity	
0	1,059,003 (63.7)
1	15,404 (9.3)
2 or more	448,835 (27.0)
Country of birth	
Sweden	1,421,169 (85.5)
Nordic countries except Sweden	27,361 (1.7)
EU except the Nordic countries	43,223 (2.6)
Europe except EU and Nordic countries	35,340 (2.1)
Asia	86,558 (5.2)
Other	48,962 (2.9)
Missing	629 (0.0)
Medical history	
Previous ectopic pregnancy	36 (0.0)
Endometriosis	11,675 (0.7)

EU, European Union.  
Data are mean±SD or n (%).

rates per method of hormonal contraception in detail. The sensitivity analysis excluding treatment episodes with a history of ectopic pregnancy (0.3%) decreased the incidence rates by 0.01–0.03 (data not shown).

The Cox regression models adjusted for history of ectopic pregnancy and endometriosis and stratified by age group are presented in Appendix 1, available online at <http://links.lww.com/AOG/C638>, showing the relatively higher predicted risk for ectopic pregnancy in women with a history of ectopic pregnancy independent of method of hormonal contraception. The highest predicted risk for ectopic pregnancy was seen in women younger than age 40 years with a previous history of ectopic pregnancy using the 13.5-mg LNG IUD. According to the model, approximately nine cases of ectopic pregnancy in 100 treatments are expected for the 13.5-mg LNG IUD during 2.5–3 years of use in this specific subset of the study population.

## DISCUSSION

In this large, population-based prospective cohort study among women of reproductive age using hormonal contraception, the risk of ectopic pregnancy was highest among the women using 13.5-mg LNG hormonal IUDs (2.76 per 1,000 woman-years) compared with all other methods of hormonal contraception, which had similar highly protective rates. The results support the findings from a hospital-based study in which low-dose hormonal IUDs were associated with lower protective effects compared with higher-dose hormonal IUDs.<sup>18</sup>

The overall incidence rate of ectopic pregnancy in the study population was low, 0.28 per 1,000 woman-years from 2005 to 2016, as compared with the average approximate incidence rate of 0.83 per 1,000 woman-years for those aged 15–49 years in the Swedish population between 2008 and 2016.<sup>6</sup> This suggests that all the hormonal contraceptives effectively prevented pregnancies to varying degrees and subsequently lowered the absolute risk of ectopic pregnancy. The current study supports previous findings that progestogen-only methods may be associated with a lesser protective effect than combined methods.<sup>16</sup> This may be explained by the fact that many women continue to ovulate during use of hormonal IUDs and oral low-dose progestogen-only pills.

When adjusting the results for previous ectopic pregnancy or endometriosis, the effect of age is clearly demonstrated, with women younger than age 40 years having a higher predicted relative risk of ectopic pregnancy independent of the use of hormonal contraception. This is expected because of their

**Table 2. Number of Treatment Episodes, Ectopic Pregnancies, and Woman-Years Per Hormonal Contraceptive Method, Sweden, 2005–2016**

Type of Hormonal Contraception	No. of Women	No. of Treatment Episodes	Median Follow-up (y)	No. of Ectopic Pregnancies	Woman-Years	Proportion of Total Woman-Years (%)	IR/1,000 Woman-Years	95% CL
Any contraceptive	1,663,242	6,807,293	0.5	1,915	6,960,110		0.28	0.26–0.29
Hormonal IUD								
13.5 mg LNG	37,539	37,731	0.87	104	37,647	0.5	2.76	2.26–3.35
52 mg LNG	434,242	523,391	3.27	522	1,719,652	24.7	0.30	0.28–0.33
Combined hormonal contraception								
Vaginal	154,265	405,432	0.29	54	206,875	3.0	0.26	0.20–0.34
Patch	40,320	77,176	0.34	20	40,979	0.6	0.49	0.30–0.75
Oral	973,704	2,932,214	0.62	566	2,790,107	40.1	0.20	0.19–0.22
Etonogestrel implant	188,257	251,232	2.16	149	479,066	6.9	0.31	0.26–0.37
Progestogen-only contraception								
Medium-dose (oral, desogestrel 75 mg)	657,078	1,783,618	0.42	286	1,181,276	17.0	0.24	0.21–0.27
Low-dose (oral, norethisterone 0.35 mg and lynestrenol 0.5 mg)	150,597	394,696	0.46	198	245,180	3.5	0.81	0.70–0.93
Medroxyprogesterone acetate injection	91,800	401,803	0.36	16	259,327	3.7	0.06	0.04–0.10
By age (y)								
Younger than 40	1,430,307	5,752,697	0.50	1,834	5,709,869		0.32	0.31–0.34
40 or older	384,403	1,054,596	0.53	81	1,250,240		0.06	0.05–0.08
Endometriosis								
No	1,651,567	6,762,183	0.50	1,904	6,915,450		0.28	0.26–0.29
Yes	12,715	45,110	0.46	11	44,660		0.25	0.12–0.44
Previous ectopic pregnancy								
No	1,663,206	6,788,680	0.50	1,827	6,945,662		0.26	0.25–0.28
Yes	6,558	18,613	0.43	88	14,448		6.09	4.88–7.50

IR, incidence rate; CL, confidence limit; IUD, intrauterine device; LNG, levonorgestrel.

higher fertility. For all subgroups, the 13.5-mg LNG hormonal IUD was associated with the lowest protective effect, most evident for the women with a history of ectopic pregnancy, which has been reported previously.<sup>15</sup>

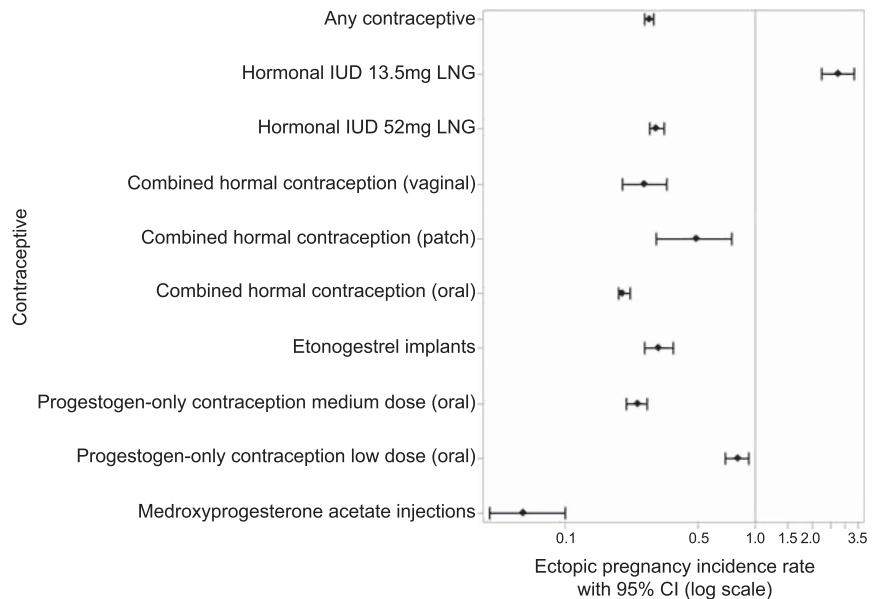
The strength of this study is its large population size, with prospectively collected data comprising all women in Sweden using hormonal contraception during the study period, assuring generalizability of the results and reduced risk of selection or recall bias. The Swedish population-based National Patient Register contains information on all inpatient and outpatient care in the Swedish hospitals, allowing information on known risk factors such as history of ectopic pregnancy or endometriosis to be included. The analyses were adjusted for women with a

diagnosis of endometriosis, a common condition, but the prevalence may be underestimated when using diagnosis data from the patient register, because severe cases of endometriosis are predominantly seen in hospitals. Consequently, the effect of endometriosis on ectopic pregnancy may be overestimated. The data were not adjusted for other known risk factors of ectopic pregnancy, including history of pelvic inflammatory disease, chlamydia infection, or tubal surgery, because none of these conditions are contraindications for the use of any of the hormonal contraceptive methods, including IUD.<sup>21,22</sup>

The limitations of the study include the lack of information on smoking in the Swedish health registers. Smoking is a possible contraindication for combined oral contraception, especially if the woman

**Fig. 2.** Crude incidence rates and 95% CIs for ectopic pregnancies per method of hormonal contraception and covariates, Sweden 2005–2016 (log scale). Progestogen-only contraception medium-dose: desogestrel 75 mg; progestogen-only contraception low-dose: norethisterone 0.35 mg and lynestrenol 0.5 mg. IUD, intrauterine device; LNG, levonorgestrel.

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is older than age 40 years. This may influence the results; however, we judge this effect to be minor. Other limitations include difficulties confirming the actual use of contraception. It is known that early discontinuation rates differ between methods of hormonal contraception.<sup>23,24</sup> In the current study it is assumed that the women are currently using the prescribed hormonal contraception if they filled a prescription valid for a certain period and have no record in the registers for indicating otherwise (such as a pregnancy related diagnosis, or removal procedure for IUD or implant). Records of filled prescriptions do not capture actual use. We therefore do not know whether or when the dispensed contraception is used but make the assumption that use, and therefore treatment time, begins on the date of dispensation. Hence, the study may underestimate the protective effect of hormonal contraception on the risk of ectopic pregnancy. Further, the Prescribed Drug Register does not include treatment without prescription (eg drugs given during inpatient care). However, because hormonal contraception is exclusively prescribed as outpatient care, the potential missed treatment episodes are assumed to be negligible in this study. The risk of missing cases of ectopic pregnancy is assumed to be small, because all cases of ectopic pregnancy in Sweden are referred to hospitals for assessment of need for surgical or medical treatment and follow-up. The 13.5-mg LNG IUD has been available on the market in Sweden since January 2014. Because our study period ended in 2016, we could not study the effects on the risk of ectopic pregnancy for the 3-

year duration of its use in the majority of the users. In a previous study from our research team, the risk of ectopic pregnancy among users of the 13.5-mg LNG hormonal IUD was highest in the beginning of use.<sup>18</sup> This may indicate a possible overestimation of the risk of ectopic pregnancy among users of the 13.5-mg LNG hormonal IUD in the current study. However, the more than fivefold relative higher incidence rate of ectopic pregnancy for the 13.5-mg LNG hormonal IUD is unlikely to be fully explained by this overestimation.

These findings are clinically relevant for providing real life evidence when providing counseling about methods of contraception to women who wish to preserve fertility. Hormonal IUDs are user-friendly and safe to use, providing women with highly effective and reversible long-acting contraception with few side effects. The results of the current study indicate that the 13.5-mg LNG hormonal IUD should not be recommended for women who are concerned about the risk of ectopic pregnancy. The 13.5-mg LNG hormonal IUD was marketed to a younger (or primiparous) population owing to its smaller size compared with the 52-mg LNG hormonal IUD. A hormonal IUD containing 19.5 mg LNG and with the same size as the 13.5-mg LNG hormonal IUD was approved for the Swedish market in November 2016. Hence, it has not been possible to study the product during the current study period. Further research is needed on the 19.5-mg LNG hormonal IUD and risk of ectopic pregnancy in real-life settings.

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