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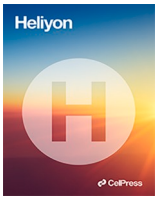

Research article

Safety profile of levonorgestrel intrauterine system: Analysis of spontaneous reports submitted to FAERS

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ABSTRACT

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an established, long-acting contraceptive option. With the widespread use of the LNG-IUS, drug-reported adverse events (AEs) have also garnered significant attention. In this study, we conducted a real-world analysis using the FDA's Adverse Event Reporting System (FAERS) database to assess the incidence of AEs associated with LNG-IUS use. Data from FAERS spanning from 2004Q1 to 2024Q1 were reviewed, with a focus on reports in which LNG-IUS was the primary suspected and secondary suspect drug. Signal detection was carried out utilizing Standardized MedDRA Queries (SMQ) and Preferred Terms (PT), with reporting odds ratio (ROR), proportional reporting ratio (PRR), and information component (IC) employed to identify Signals of Disproportionate Reporting (SDR) for AEs. A positive SDR was defined when all three methods indicated significance. Analysis of 13 SMQs revealed notable SDRs in ear and eye disorders, cardiac arrhythmias, and lipodystrophy. Of the 61 suspected SDRs identified at the PT level, nearly half were not previously documented in labeling. Key potential signals of AEs associated with LNG-IUS use included increased heart rate, papilledema, idiopathic intracranial hypertension, cervical dysplasia, ruptured ovarian cyst, and uterine embedment and perforation. The findings underscore the importance of signal detection using FAERS data for identifying safety concerns related to LNG-IUS. Long-term observational studies are warranted to confirm and further elucidate these potential safety signals.

1. Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a T-shaped plastic intrauterine device that is placed in the uterus to slowly release the drug levonorgestrel. It has been on the market since the mid 1990s in most European countries and since 2001 in the USA [1,2]. LNG-IUS has versatile applications beyond contraception. It is also utilized for the management of heavy menstrual bleeding (HMB), treatment of endometriosis, and as a means of providing endometrial protection during estrogen replacement therapy [3–5].

The 52-mg LNG-IUS recently received approval by the US Food and Drug Administration (FDA) for the prevention of pregnancy for

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up to 7 years [6]. With the increasing use and extended duration of use of the LNG-IUS, drug-reported adverse events (AEs) have also gained significant attention. Common complications associated with LNG-IUS insertion include failed insertion, pain, infection, menstrual abnormalities, and expulsion [7]. Rare but serious complications such as intracranial hypertension [8], ectopic pregnancy [9], uterine perforation [10], pelvic inflammatory disease (PID), or infections [11]. It is worth noting, research has identifiified the important role that progesterone plays in breast cancer. Studies evaluating the association between LNG-IUS use and breast cancer risk have yielded conflicting results. Some studies suggest a potential increased risk of breast cancer with LNG-IUS use, while others do not find a significant association [12,13]. Moreover, the post-marketing safety of the LNG-IUS has not been systematically analyzed based on large-sample real-world studies. Therefore, the long-term large-sample post-marketing risk studies of LNG-IUS are urgently needed.

The FDA Adverse Event Reporting System (FAERS) is a comprehensive database that collects reports of adverse events (AEs), medication errors, and product quality complaints submitted to the FDA. This database plays a critical role in post-marketing safety surveillance for drugs. In order to effectively identify signals of AEs, data mining methods such as disproportionality analyses utilizing Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) calculations are employed. Therefore, the objective of this study was to detect and analyze Signals of Disproportionate Reporting (SDRs) of AEs associated with the use of LNG-IUS, with the aim of exploring the occurrence of rare but serious AEs in real-world settings.

2. Material and methods

2.1. Data source

We conducted a retrospective pharmacovigilance study using data from the FAERS database through the Open Vigil FDA platform, which covers the period from January 2004 to March 2024. The Open Vigil FDA is a front-end interface developed by Dr. Ruwen Böhm since 2014, providing access to the open FDA interface. It is implemented as a single PHP (PHP Hypertext Preprocessor) program file. This platform allows for the extraction of the latest reports and provides a user interface for general data extraction, report counting, and analysis, as well as specialized interfaces for clinically relevant scenarios. The data is presented in tables in various output formats, such as human-readable HTML, a spreadsheet-like format (comma-separated values, CSV), or other forms like JSON and XML [14]. The database contained a total of 13,654,733 reports, providing substantial support for post-market research. We utilized Drugs.com, a comprehensive and current online resource for drug information, to confirm the specific drug name. Our analysis centered on reports associated with the "levonorgestrel-releasing intrauterine system" as the primary suspect and secondary suspect.

2.2. Definition of adverse events

AEs reported in FAERS are categorized using preferred terms (PTs) within the Medical Dictionary for Regulatory Activities (MedDRA) terminology (https://www.meddra.org/standardised-meddra-queries). MedDRA follows a straightforward 5-level hierarchical structure, including System Organ Classes (SOC), High-Level Group Terms (HLGT), High-Level Terms (HLT), Preferred Terms (PT), and Lowest Level Terms (LLT). This classification system enables a systematic organization of AEs. Furthermore, the Standard MedDRA Analysis Query (SMQ) tool provided by MedDRA plays a crucial role in identifying drug-induced clinical diseases by considering clinical diagnosis and treatment factors. SMQs are a set of terms designed based on specific medical themes or concepts to assist researchers in identifying and categorizing adverse events related to that theme. In comparison, preferred terms (PT) are basic terms within the MedDRA system used to describe specific medical concepts or clinical conditions. While the PT level is often utilized for indexing signals, it is not always the optimal choice. In certain cases, aggregating MedDRA terms based on syndromes or diagnoses has shown to be more effective in detecting signals at an earlier stage [15]. For this study, we relied on the definitions provided by MedDRA, and the AE signals associated with LNG-IUS were detected and analyzed using both the SMQ and PT levels.

2.3. Data mining algorithm and statistical analysis

In this study, a descriptive analysis was conducted to examine the fundamental characteristics of AEs reported for LNG-IUS in the FAERS database. To identify signals of disproportionate reporting (SDR), three methods were employed: reporting odds ratio (ROR), proportional reporting ratio (PRR), and information component (IC). If all three methods indicated positive SDRs, it was considered as a positive SDR. These methods are based on a two-by-two contingency table approach, and the equations and criteria used for the three algorithms can be found in Tables 1 and 2 [16–19]. Statistical analysis was performed using SPSS 23.0, and the frequency (%) was used to express the statistical data. Also, Logistic regression was employed to identify risk factors. A statistical significance can be assumed when the lower limit of the 95 % confidence interval (CI) of the ROR is greater than one.

3. Results

3.1. Descriptive analysis

A total of 13,654,733 adverse event (AE) reports were submitted to FAERS between 2004Q1 and 2024Q1, with 124,214 reports indicating LNG-IUS as the primary suspected drug. Table 3 provides a description of the characteristics of AE reports associated with LNG-IUS. The majority of patients affected were in the age range of 18–44 years (68.71 %), and the reports were primarily submitted by consumers. Notably, serious adverse events (SAEs) accounted for 11.30 % of the reports, with 8.33 % involving hospitalization

(initial or prolonged) and 1.48 % resulting in disability. The top three concomitant medications reported in association with LNG-IUS were Ibuprofen, Xyrem, and Sertraline. Logistic regression results showed that only age distribution between 45 and 64 and consumer or non-health professional reporting had a statistical significance ($p < 0.05$) indicating an association with the occurrence of AEs (Table 4).

3.2. The SMQs most frequently reported with the use of LNG-IUS

Table 5 presents the SMQs that were most frequently reported in association with the use of LNG-IUS, ranked based on the number of reports. A total of 13 SMQs were identified, with a notable SDR observed for ear and eye disorders including optic nerve disorders (ROR = 16.53), functional lactation disorders (ROR = 1.45), retinal disorders (ROR = 3.63), as well as hearing and vestibular disorders (ROR = 13.71). Additionally, cardiac arrhythmias (ROR = 14.13) and lipodystrophy (ROR = 9.40) were identified as significant SDR. Other SMQs including pregnancy and neonatal outcomes (ROR = 4.03), as well as angioedema (ROR = 8.41).

3.3. Signal of preferred terms

Further analysis conducted at the PT level revealed 61 suspicious SDRs, out of which 28 (45.90 %) were not included in the label. The AEs induced by LNG-IUS were primarily concentrated in the following organ systems: product issues, reproductive system and breast disorders, pregnancy, puerperium and perinatal conditions, and the nervous system. Notably, This study shows some pairs AEs-LNG-IUS as potential signals: including increased heart rate, cervical dysplasia, ruptured ovarian cyst, and breast mass, uterine embedment and perforation, uterine rupture, papilledema, idiopathic intracranial hypertension, and ruptured ectopic pregnancy. In addition, this study suggests that breast cancer and endometrial cancer also indicate suspicious SDRs.

4. Discussion

LNG-IUS is commonly used in women of reproductive age for both contraceptive and non-contraceptive purposes. However, despite its benefits and effectiveness, approximately 40 % of women discontinue LNG-IUS treatment, primarily due to AEs [20]. In this study, we reviewed AE reports submitted to the FAERS database to investigate the safety profiles of LNG-IUS. To the best of our knowledge, this is the first study to examine the potential AE of LNG-IUS using three different pharmacovigilance methods. Overall, our analysis revealed five main findings: 1) Apart from product and reproductive system issues, LNG-IUS may also induce systemic AEs, including cardiac, eye, gastrointestinal, and nervous system disorders; 2) Device dislocation and expulsion were identified as frequent AEs reported with LNG-IUS use. Unnoticed dislocation or expulsion of the device can lead to unplanned pregnancy, with a high risk of ectopic pregnancy. Additionally, this study also suggests an may increased risk of uterine perforation with the intrauterine device; 3) The use of LNG-IUS may increase the risk of infection, such as pelvic inflammatory disease, vaginal infection, and endometritis. However, there was no evidence of an increased risk of infective endocarditis; 4) We observed strongly positive SDR related to idiopathic intracranial hypertension, with presenting symptoms including papilledema, tinnitus, diplopia, and visual field defects; 5) Users of LNG-IUS should be aware of potential adverse events such as breast swelling, breast cysts, and galactorrhea. Our results also did suggest a significant link between LNG-IUS and breast cancer female and endometrial cancer. These findings provide valuable insights into the safety profile of LNG-IUS and highlight the importance of monitoring and managing potential AEs associated with its use. Further long-term observational data will be necessary to better characterize this unconfirmed potential safety signal.

Device dislocation and expulsion are major concerns in patients using LNG-IUS, as unnoticed expulsion can lead to unplanned pregnancies and increased medical costs [21]. In our study, we found that out of the total AEs reported, 39653 cases were device expulsion (31.92 %) and 15547 cases were device dislocation (12.52 %). Device expulsion is a common AE associated with LNG-IUS use, often occurring early after treatment initiation, with reported rates of partial or complete expulsion ranging from 4.4 % to 9.9 % [22,23]. In a systematic review in which the authors assessed 20 studies conducted with nulliparous women, users of the Cu-IUD presented more expulsions in 13 out of 20 studies. Nevertheless, this is a controversial issue, as later studies have found no difference in the expulsion rate between nulligravidas and parous women fifitted with a Cu-IUD or a LNG-IUS [21,24]. Several risk factors have been identified for device expulsion, including underlying uterine lesions such as adenomyosis and uterine leiomyomas, symptoms such as heavy menstrual bleeding (HMB) and dysmenorrhea, and prior treatment with a GnRH agonist before insertion. Additionally, expulsion of the LNG-IUS is more common among women with submucosal myomas (15.4 %) compared to those with other types of myomas (7.9 %) or without a myoma (4.2 %) [25,26]. Furthermore, the overall expulsion rate within three months of immediate LNG-IUS insertion following medical termination of pregnancy is higher compared to delayed insertion [27]. In general, LNG-IUS use would reduce the risk of ectopic pregnancy (compared with non-contraceptive users), but if the LNG-IUS users become pregnant, there is a higher risk of ectopic pregnancy. In the case of pregnancy occurring with LNG-IUS use, approximately 25%–50 % of these pregnancies are ectopic [28]. Our study also found a strong SDR for ectopic pregnancy associated with LNG-IUS use (ROR = 51.18, PRR = 50.59, IC = 5.10), which is consistent with previous research [29,30]. These findings highlight the importance of considering the possibility of ectopic pregnancy in patients with LNG-IUS implantation, particularly if they present with symptoms such as abdominal pain. Overall, our study provides important insights into the AE related to device expulsion and dislocation with LNG-IUS use, emphasizing the need for careful monitoring and management to ensure the safety and effectiveness of this contraceptive method.

Currently, there is ongoing debate regarding whether LNG-IUS increases the risk of pelvic infection. Previous studies have shown conflicting results. In a meta-analysis published in 1992, which included nearly 23,000 parous women (with 74 % of them using a

copper intrauterine system), there was a suggested increased risk of pelvic infection within the first three weeks following intrauterine system placement [31]. However, subsequent studies using survival analysis have shown that LNG-IUS users have lower rates of discontinuation due to pelvic inflammatory disease (PID) compared to copper users. The overall rate of pelvic infection over a two-year period remained similar at 0.6 %, and most cases of pelvic infection can be successfully treated with outpatient antibiotics, typically not requiring removal of the intrauterine system [32,33]. In our study, we observed a strong association between LNG-IUS use and pelvic inflammatory disease (ROR = 102.37, PRR = 92.46, IC = 4.82) as well as endometritis (ROR = 12.42, PRR = 12.21, IC = 2.13). Other infections reported included vaginal infection, bacterial vaginitis, and vulvovaginal mycotic infections. The risk of pelvic infection and infectious endocarditis from transient bacteremia after insertion of an LNG-IUS is a concern in these women [34]. A study evaluate efficacy and safety of levonorgestrel 52 mg intrauterine system (IUS) during years 7 and 8 of use showed that pelvic infection was diagnosed in 16 (0.9 %) participants during IUS use, 1 each in years 7 and 8 [35]. These findings highlight the need for further research and careful monitoring of pelvic infections in LNG-IUS users. While the overall risk of pelvic infection remains relatively low and can be effectively treated with antibiotics, healthcare providers should remain vigilant and promptly address any signs or symptoms of infection in women using LNG-IUS.

Intracranial hypertension (ICH) is characterized by symptoms such as transient visual obscurations, tinnitus, severe headaches, or emesis [36]. Certain medications, including tetracycline and minocycline, have been associated with secondary ICH [37,38]. In our study, we identified 564 patients with idiopathic intracranial hypertension and 244 patients with benign intracranial hypertension who were using an LNG-IUS. The mean age of these patients was 33 years (range, 18 to 56). Furthermore, we observed a high risk of papilledema, tinnitus, diplopia, and visual field defects in association with LNG-IUS use in our study. We also found a high ROR value for retinal disorders, hearing and vestibular disorders, optic nerve disorders, and angioedema in the Standardized MedDRA Queries (SMQs). In 1995, Alder described fifty-six women with ICH who had received levonorgestrel contraceptive implants (Norplant®) [39]. Most reports of ICH secondary to progestins have been associated with levonorgestrel and medroxyprogesterone [39,40]. A previous study showed that women using an LNG-IUS may have an increased risk of developing ICH, although it is not considered an independent risk factor. The prevalence of ICH was approximately 0.18 % and 0.15 % in the LNG-IUS population compared to 0.02 % and 0.04 % in the non-LNG-IUS population. The reported odds ratios (ORs) for ICH and papilledema with LNG-IUS (Mirena®) were 1.78 (95 % confidence interval [CI] 1.41–2.25) and 1.50 (95 % CI 1.10–2.05), respectively. It has been hypothesized that LNG-IUS could potentially increase intracranial pressure through mechanisms such as vitamin A metabolism or venous microthrombi [41]. Moreover, obesity itself is considered an independent risk factor for increased intracranial pressure. In our study, we also observed a high relative odds ratio (ROR) for weight gain in association with LNG-IUS use [39]. Furthermore, drug-induced obesity could potentially contribute to the development of ICH. It is important to note that the incidence of LNG-IUS-induced ICH may be underestimated due to limited awareness. Therefore, future studies are warranted to validate and further explore these findings.

Large-scale epidemiological studies have consistently demonstrated an increased risk of breast cancer associated with certain hormonal contraceptive methods, particularly when used for extended durations [42]. However, the precise role of progesterone in breast carcinogenesis remains poorly understood. The potential association between the use of LNG-IUS and breast cancer risk is still a matter of theoretical consideration [43]. In our study, we did identify positive SDRs for breast tenderness, breast cysts, and galactorrhea. we also did observe an elevated risk of breast cancer female and endometrial cancer among patients using LNG-IUS. A recent meta-analysis, which included two cohort studies and two case-control studies, reported no increased risk of breast cancer among users of LNG-IUS, both before and after menopause [44]. However, another systematic review and meta-analysis suggested a potential heightened risk of breast cancer among LNG-IUS users, with an odds ratio (OR) of 1.16 (95 % CI 1.06–1.28, I2 = 78 %, $P < 0.01$), particularly among women aged 50 years or older [42]. It is important to note that postmenopausal hormone replacement therapy has also been associated with an increased risk of breast cancer, making it challenging to discern the potential biological effects of LNG-IUS in postmenopausal women who are concurrently using hormone replacement therapy [42]. Consequently, further research is warranted to better understand the potential association between LNG-IUS use and breast cancer risk.

Uterine perforation is a relatively rare but well-documented complication of LNG-IUS, with uterine embedment and perforation occurring in approximately 1 in 1000 insertions [7]. In our study, we observed 6548 cases of uterine embedment and perforation, which is a highly significant finding. A recent large-scale multicenter cohort study identified 1008 cases of uterine perforation among 326,658 individuals using intrauterine devices [45]. Furthermore, this study revealed that the risk of uterine perforation within 4 days–6 weeks postpartum is nearly seven times higher compared to non-postpartum insertion [45]. Several risk factors for uterine perforation have been identified, including breastfeeding, postpartum amenorrhea, ≤6 months postpartum, and provider inexperience [29,46]. Symptoms of embedment and/or perforation can range from asymptomatic to severe abdominal pain and abnormal vaginal bleeding [47,48]. In rare cases, there may be migration of the device into the intraabdominal space, potentially leading to injury to various pelvic and abdominal structures [7]. These findings underscore the importance of careful follow-up and monitoring, particularly among high-risk groups for uterine perforation.

In 2017, a study showed that heart rate was significantly potentiated during the Trier Social Stress Test (TSST) in women using LNG-IUD [49]. In our study, we did identify positive SDRs for Cardiac arrhythmias in SMQs and increased heart rate in PT level. But no clinically significant cardiovascular event was identified during the 1 year after 52-mg LNG-IUS insertion among women with cardiovascular disease [50]. The association of LNG-IUD in the cardia requires more clinical studies.

5. Limitations

There are several limitations to consider in our study. Firstly, the assessment of LNG-IUS safety did not take into account the primary disease of the patients, the potential interaction of drug combinations, and the individual liver and kidney function status.

These factors can influence the overall safety profile of LNG-IUS and should be considered in future studies. Secondly, our study only suggests a statistical association between LNG-IUS and AEs. Further assessment and validation are needed to determine the actual risk of AEs associated with LNG-IUS use. It is important to conduct more comprehensive and rigorous studies to establish a clearer understanding of the safety profile of LNG-IUS. Thirdly, the FAERS database contains only cases with AEs. The incidence rate of each AEs cannot be calculated because of lacking total numbers of patients receiving LNG-IUS treatment. The age distribution of the patients in our study had a substantial proportion (34.63 %) with unknown age, which could potentially compromise the representativeness of the overall age distribution. Moreover, it is noteworthy that the reports on LNG-IUS were primarily sourced from consumers or non-health professionals (50.80 %), thereby warranting caution regarding the quality and reliability of the reported information. Additionally, it is important to acknowledge that the reporting of AEs in the database may be subject to report duplication, underreporting, missing data, and incomplete information. This can potentially impact the accuracy and reliability of our results. In conclusion, this study provides a new perspective on evaluating the safety of LNG-IUS. Despite the limitations mentioned, it highlights the importance of considering various factors in assessing the safety profile of LNG-IUS and emphasizes the need for further research in this area. By doing so, we can enhance the safety consciousness among medical professionals and reduce the potential risks associated with LNG-IUS use in clinical practice.

6. Conclusion

Our findings underscore the importance of signal detection using FAERS data for identifying safety concerns related to LNG-IUS. Long-term observational studies are warranted to confirm and further elucidate these potential safety signals.

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Ethics approval

This article does not contain any studies with human participants or animals perormed by any of the authors.

Data availability statement

Data is available upon request.

CRediT authorship contribution statement

Lin Chen: Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization. **Rui Bao:** Methodology, Formal analysis, Data curation. **Xiaojiang Tian:** Writing – review & editing, Validation, Project administration, Data curation, Conceptualization.

Declaration of competing interest

Neither the entire manuscript nor any part of its content has been published or has been accepted elsewhere and this manuscript has not been submitted to any other journal. No portion of the text has been copied from other material in the literature. All of the authors in this manuscript have read and approved the final version submitted, and there are no conflicts involved in this submission.

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Appendices.

Table 1
Two-by-two contingency table for disproportionality analyses

	Reports with the target AE	All other AEs	Total
Reports with the target drug	a	b	a+b
All other drugs	c	d	c + d
Total	a+c	b + d	a+b + c + d

M = #reports with LNG-IUS.
N = #reports with event in database.
D = #reports in database.
a = #reports with LNG-IUS and event.
b = #N-a.
c = #M-a.
d = #D-a-b-c.

Table 2
Summary of major algorithms used for signal detection.

Algorithms	Equation	Criteria
ROR	ROR = (a/b)/(c/d)	95 % CI > 1, N ≥ 3
PRR	PRR = (a/(a + c))/(b/(b + d))	PRR ≥2, χ2≥4, N ≥ 3
BCPNN	IC = log2a (a + b + c + d)/((a + c) (a + b))	IC-2SD > 0

Table 3
Characteristics of adverse event reports

	AE reports	(%)
Age (year)		
<18	1532	1.23 %
18–44	85342	68.71 %
45–64	10432	8.40 %
65–74	156	0.13 %
≥75	43	0.03 %
Unknown	26709	21.50 %
Individual submitting		
Consumer or non-health professional	60242	48.50 %
Physician	30942	24.91 %
Pharmacist	4232	3.41 %
Other Health professionals	19432	15.64 %
Lawyer	4293	3.46 %
Unknown	5073	4.08 %
Serious outcomes		
Death	231	0.19 %
Hospitalization-initial or prolonged	10342	8.33 %
Disabling	1834	1.48 %
Life Threatening	1632	1.31 %
Concomitant drug(Top five)		
Ibuprofen	832	0.67 %
Xyrem	673	0.54 %
Zoloft	439	0.35 %
Synthroid	397	0.32 %
Vitamin D	632	0.51 %

Table 4
Logistic regression results of risk factors for the occurrence of AEs

Variables	β	SE	Wald	p	Odds ratio	95 % CI
Age						
<18	0.007	0.012	0.296	0.586	1.007	0.983–1.031
18–44	0.016	0.014	1.280	0.258	1.016	0.988–1.045
45–64	0.735	0.276	7.107	0.008	2.086	1.215–3.580
65–74	0.041	0.025	1.004	0.563	1.213	0.921–2.012
≥75	0.036	0.085	0.841	0.321	1.011	0.872–1.621
Individual submitting						
Consumer or non-health professional	0.735	0.276	7.107	0.008	2.086	1.215–3.580
Physician	0.073	0.013	1.711	0.198	1.113	0.922–2.193
Pharmacist	0.008	0.042	0.341	0.652	1.004	0.731–1.123
Other Health professionals	0.001	0.011	0.531	0.831	1.101	0.531–1.841
Lawyer	0.083	0.023	3.313	0.731	1.319	0.341–2.413
Concomitant drug(Top five)						
Ibuprofen	0.312	0.134	1.421	0.211	1.413	0.452–1.932
Xyrem	0.123	0.412	0.313	0.093	1.341	0.582–2.365
Zoloft	0.419	1.421	0.471	0.631	1.041	0.513–3.521
Synthroid	0.294	1.462	1.003	0.071	1.054	0.451–4.513
Vitamin D	0.264	2.602	1.735	0.193	1.457	0.422–3.003

Table 5
The frequently reported SMQs of LNG-IUS-AEs

SMQs	N	ROR (95 % two-sided CI)	PRR (χ2)	IC (IC-2SD)	Label
Hemorrhage terms	10038	3.87 (3.79–3.96)	3.11 (1711.97)	1.52 (1.49)	Yes
retroperitoneal fibrosis	5828	3.65 (3.55–3.75)	3.32 (9831.40)	1.02 (1.00)	No
Gastrointestinal nonspecific inflammation and dysfunctional conditions	4724	1.85 (1.65–2.41)	1.71 (852.04)	0.82 (0.80)	Yes
Pregnancy and neonatal topics	4599	4.03 (3.91–4.16)	3.72 (941.92)	1.79 (1.78)	Yes
Retinal disorders	2005	2.58 (2.01–5.17)	2.41 (6310.3)	1.54 (1.52)	Yes
Lipodystrophy	1521	9.40 (9.14–11.19)	9.38 (9378.30)	3.68 (3.65)	No
Cardiac arrhythmias	1233	14.13 (12.13–18.28)	14.01 (5713.11)	4.45 (4.31)	No
Hearing and vestibular disorders	641	1.85 (1.62–2.48)	1.84 (562.1)	0.75 (0.72)	No
Optic nerve disorders	481	16.53 (10.31–15.19)	16.49 (4125.00)	4.25 (4.19)	No
Peripheral neuropathy	387	2.74 (2.29–3.27)	2.74 (133.01)	1.41 (1.37)	No
Ocular motility disorders	349	1.65 (1.10–1.94)	1.61 (141.02)	0.84 (0.80)	No
Angioedema	245	8.41 (3.47–7.37)	8.34 (584.92)	2.84 (2.64)	No
functional lactation disorders	118	13.71 (11.38–16.51)	12.94 (1294.4)	3.04 (3.01)	No

SMQ: standardized MedDRA query.
N: The number of adverse events reports.
ROR: reporting odds ratios.
PRR: proportional reporting ratio.
IC: information component.
SD: Standard Deviation.

Table 6
Signal strength for LNG-IUS-AEs at the PT level in FAERS

SOC System	PTs	N	ROR (95 % two-sided CI)	PRR (χ2)	IC (IC-2SD)	Label
Cardiac	Increased Heart Rate	1241	1.87 (1.65–2.39)	1.86 (527.51)	0.88 (0.87)	No
Ear and labyrinth	Tinnitus	538	2.41 (1.97–2.84)	2.35 (417.55)	0.88 (0.85)	Yes
	Papilledema	384	12.31 (10.59–18.27)	12.14 (3941.28)	2.55 (2.51)	No
	Diplopia	347	1.82 (1.15–2.83)	1.75 (34.97)	0.45 (0.43)	No
	Visual field defect	162	1.63 (1.42–3.97)	1.62 (83.23)	0.93 (0.91)	No
Gastrointestinal	Abdominal pain	13214	5.61 (5.51–5.72)	5.05 (42123.65)	2.29 (2.27)	Yes
	Abdominal distension	1623	2.95 (2.73–3.20)	3.04 (782.46)	1.23 (1.20)	Yes
	emesis	1614	1.73 (1.65–1.82)	1.72 (483.15)	0.77 (0.76)	Yes
	Abdominal pain lower	6166	58.68 (56.89–60.54)	55.38 (22184.74)	5.22 (5.20)	Yes
	abdominal adhesions	17	3.07 (1.90–4.95)	3.04 (21.33)	0.43 (0.41)	No
General disorders and administration site conditions	Post procedural discomfort	1762	102.36 (89.61–132.92)	93.31 (6382.93)	3.12 (3.08)	Yes
	Night sweats	432	1.72 (1.38–2.47)	1.23 (42.31)	0.31 (0.30)	Yes
Infections and infestations	Pungal Infection	431	1.21 (1.09–1.86)	1.18 (89.43)	0.53 (0.50)	No
Injury, poisoning and procedural complications	Post procedural hemorrhage	3173	34.32 (23.14–50.31)	32.31 (62718.42)	3.91 (3.88)	Yes
Nervous system	Idiopathic intracranial hypertension	564	113.81 (78.08–150.23)	109.31 (41323.93)	5.23 (5.21)	No
	Benign intracranial hypertension	244	20.22 (18.49–26.16)	21.32 (3213.34)	4.09 (4.01)	No
Pregnancy, puerperium, and perinatal conditions	pregnancy with contraceptive device	2311	147.94 (140.31–155.98)	86.65 (19654.20)	8.94 (8.92)	No
	Ectopic pregnancy	1289	51.18 (47.92–54.68)	50.59 (43223.44)	5.10 (5.05)	Yes
	Ruptured ectopic pregnancy	263	85.82 (75.32–105.82)	85.02 (1253.53)	5.46 (5.39)	No
Product issues	Device expulsion	39653	225.80 (221.22–230.57)	142.28 (168401.95)	5.84 (5.80)	No
	Device dislocation	15547	172.53 (130.19–197.72)	103.46 (533244.90)	7.63 (7.67)	No
	Complication of device insertion	2504	57.46 (54.75–60.31)	56.15 (90554.06)	5.22 (5.19)	No
Reproductive system and breast disorders	Utering embedment and perforation	6548	745.24 (678.62–835.43)	715.32 (754345.87)	6.89 (6.84)	No
	Vaginal hemorrhage	6336	28.01 (27.24–28.81)	26.43 (125885.65)	4.43 (4.41)	Yes
	Amenorrhea	4382	80.54 (48.42–84.46)	57.34 (132496.44)	6.83 (5.78)	Yes
	Pelvic pain	3910	34.06 (32.14–39.31)	33.87 (543243.76)	3.56 (3.51)	Yes
	Menorrhagia	3304	23.13 (21.88–25.31)	21.37 (542342.42)	2.87 (2.83)	Yes
	Dyspareunia	1721	104.13 (98.72.53–118.93)	101.23 (98363.55)	5.12 (5.09)	No

(*continued on next page*)

Table 6 (*continued*)

SOC System	PTs	N	ROR (95 % two-sided CI)	PRR (χ2)	IC (IC-2SD)	Label
	Ovarian cyst	1923	24.24 (18.31–30.15)	23.24 (42134.2)	4.05 (4.01)	Yes
	heavy menstrual bleeding	1456	27.63 (26.15–29.19)	24.08 (32374.20)	4.21 (4.18)	Yes
	Vaginal discharge	1420	25.01 (23.23–27.52)	24.63 (25849.43)	4.33 (4.30)	Yes
	Loss of libido	1527	30.62 (27.46–37.42)	28.42 (1234.47)	4.02 (4.00)	No
	Metrorrhagia	1431	9.13 (8.21–11.42)	7.41 (8323.53)	2.31 (2.24)	Yes
	utering rupture	1053	253.79 (201.12–281.28)	179.45 (87546.84)	8.45 (8.14)	Yes
	Breast pain	1832	10.34 (9.57–13.19)	9.47 (10475.31)	4.21 (4.18)	Yes
	Dysmenorrhoea	1732	15.34 (12.83–19.42)	12.45 (7383.46)	3.54 (3.51)	Yes
	Vaginal infection	1345	17.83 (12.43–19.21)	12.43 (4324.33)	3.41 (3.31)	Yes
	Hypomenorrhoea	864	77.43 (63.24–95.67)	73.53 (50323.54)	3.84 (3.79)	Yes
	Breast tenderness	793	12.12 (6.12–16.42)	8.36 (6352.35)	3.02 (2.94)	Yes
	Coital bleeding	836	163.88 (138.46–189.26)	146.36 (52628.46)	4.26 (4.22)	No
	Pelvic inflammatory disease	745	102.37 (89.45–124.52)	92.46 (46352.34)	4.82 (4.72)	Yes
	Uterine spasm	531	50.31 (41.33–55.31)	45.32 (42422.45)	4.41 (4.32)	Yes
	Polymenorrhoea	394	23.21 (21.32–27.31)	22.13 (6724.42)	4.19 (4.02)	Yes
	Adnexa uteri pain	352	32.42 (21.31–44.21)	28.42 (23244.14)	4.21 (4.42)	Yes
	Vaginal odour	303	38.23 (23.08–42.32)	32.34 (8839.44)	3.24 (3.20)	No
	Vulvovaginal pain	554	12.22 (8.32–12.31)	9.99 (3224.32)	2.45 (2.39)	No
	Hormone level abnormal	469	10.22 (6.33–11.33)	9.32 (1673.45)	3.13 (3.09)	Yes
	Vaginitis bacterial	452	23.42 (18.32–53.21)	20.52 (4232.42)	2.22 (2.18)	Yes
	Breast Cyst	356	11.93 (10.46–15.18)	10.93 (4323.45)	3.12 (3.09)	No
	breast cancer female	284	3.03 (2.70–3.41)	2.99 (377.96)	0.42 (0.40)	No
	vulvovaginal discomfort	278	6.15 (4.53–8.89)	5.42 (1753.67)	1.54 (1.52)	No
	Vulvovaginal mycotic infections	206	6.34 (4.31–10.42)	6.10 (893.42)	1.64 (1.59)	Yes
	Ruptured Ovarian Cyst	192	22.18 (18.34–32.34)	22.03 (4323.57)	3.79 (3.75)	No
	Vulvovaginal Pruritus	183	4.12 (3.23–7.83)	4.22 (647.56)	2.01 (1.93)	Yes
	Breast Mass	164	1.45 (1.11–2.59)	1.41 (163.34)	1.32 (1.29)	No
	Endometritis	143	12.42 (10.42–40.43)	12.21 (4322.34)	2.13 (2.09)	No
	Galactorrhoea	120	2.01 (1.23–2.75)	2.00 (64.42)	0.98 (0.97)	No
	endometrial cancer	38	7.00 (3.23–9.42)	7.00 (4637.42)	0.42 (0.39)	No
Skin and subcutaneous tissue disorders	Hypertrichosis	453	23.45 (20.11–30.83)	22.73 (6746.46)	3.48 (3.46)	Yes
	diffuse alopecia	243	11.71 (9.33–18.14)	10.68 (6542.66)	3.71 (3.67)	No
Investigations	Weight increased	4367	2.68 (2.14–4.67)	2.54 (2346.76)	1.00 (0.98)	Yes

N: The number of adverse events reports.
SOC: System Organ Class.
PT: preferred terms.
ROR: reporting odds ratios.
PRR: proportional reporting ratio.
IC: information component.
SD: Standard Deviation.

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