Original Article

Safety and performance of a levonorgestrel-releasing intrauterine contraceptive device : one-year outcomes of Fiona-1 clinical registry

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The objective of the Fiona-1 registry (CTRI/2016/03/006781) is to assess the safety and performance of levonorgestrel-releasing intrauterine device (LNG-IUD), Fiona. This was a prospective, open-label, single-arm study conducted at 19 centers in India. Healthy sexually active women (aged 19-40 years) having regular menstrual cycles had the insertion of Fiona LNG-IUD. All enrolled women were followed up at 1, 3, 6 and 12 months. The primary endpoint was failure of contraception defined as occurrence of intra-uterine or ectopic pregnancy in presence of study device or due to auto-expulsion of study device. Continuation rates, reasons leading to discontinuation, adverse events (AEs) and the pharmacokinetic profile (for a subset of 27 women) were evaluated. Amongst 309 parous women, implanted with LNG-IUD, clinical follow-up (FU) at 12-month was achieved in 294 women. During 12-month FU, no intra-uterine or ectopic pregnancy was observed. There wasn't any intra- or post-procedure perforation of uterus, endometrium or myometrium injury, pelvic inflammation or device expulsion (partial or full) reported till 12-month. The continuation rate of the LNG-IUD at 12-month is reported 95.47%. None of the women experienced any serious adverse event. However, 12 (3.9%) women discontinued the study due to AE. At 12-month FU, total 30 AEs were reported. The most commonly observed AEs were bleeding problems (11/30), abdominal pain (6/30), and spotting (5/30). Pharmacokinetic profile revealed levonorgestrel concentrations of 275.08±104.03 pg/mL and 227±84 pg/mL at 1 and 6 months, respectively. The results of this study demonstrated effective contraception and favorable safety profile of Fiona LNG-IUD over 12 months.

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The levonorgestrel-releasing intrauterine device (LNG-IUD) is one of the most effective methods of contraception; however, its uptake varies widely by country[1]. The use of LNG-IUD in a wide range of women,

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regardless of age and parity, requires minimal maintenance. Besides the contraceptive effect, LNG-IUD provides potential therapeutic benefits for a range of gynecological conditions including menorrhagia, symptomatic fibroids, endometriosis, and endometrial suppression with no systemic physiological effects[2].

Improvement in contraceptive services and uptake is crucial in India where a high unintended pregnancy incidence of 70 per 1000 had been reported. According to an estimate, in India, 13% of married women have an unmet need for contraception and 6% of married women use traditional methods of contraception with relatively high failure rates[3]. Globally 14.3% women in child-bearing age use intrauterine contraception. However, National Family Health Survey reported only 1.5% IUD user rate in India[4,5]. Nevertheless, the reported low IUD user rates explained by various reasons, such as poor accessibility, few competing brands and high cost, which underscore the need for safe, affordable LNG-IUD variants to meet women's contraceptive needs. Low utilization of LNG-IUD limits the evidence of its safety and performance in Indian women. Although several studies of LNG-IUD were conducted previously, their research focused on other indications of LNG-IUD, ie, menorrhagia, abnormal uterine bleeding, uterine leiomyoma[6-8].

The Fiona (Meril Endo-Surgery Pvt Ltd, Vapi, India) is a T-shaped, 52 mg LNG-IUD with a 20 µg/day release rate indicated for contraception up to 5 years. The main objective of the present study was to evaluate the safety and performance of a new contraceptive, Fiona LNG-IUD. The secondary objective was to perform a pharmacokinetic evaluation of plasma LNG concentration up to 5 years. This publication presents the 12-month interim results of the study.

Material and Method

Study design and population :

This open-label, prospective, single-arm, post-marketing study was conducted at 19 centers in five cities across India. This study protocol was reviewed and approved by Independent Ethics Committee and the study was conducted in accordance with the Declaration of Helsinki. The trial was registered at Clinical Trials Registry of India (CTRI/2016/03/006781).

The study enrolled 309 women between April 2016 and July 2017 who were willing to opt for long acting reversible contraceptives. The study included healthy females; aged between 19-40 year; having regular menstrual cycles (21-35 days); sexually active and in a mutually monogamous relationship for at least 6 months before enrolling in the study. Key exclusion criteria were: (1) a known or suspected pregnancy; (2) currently breastfeeding women; (3) history of trophoblastic disease, ectopic pregnancy or hydatidiform mole, pelvic inflammatory disease (PID), suspicion of malignancy of genital tract; (4) positive human immunodeficiency virus (HIV) test, Venereal Disease Research Laboratory (VDRL) test or gonorrhea; (5) congenital or acquired uterine abnormalities; (6) current genital infection, allergy to LNG or any component of intrauterine device.

Women who want long term contraception (and if required, her spouse) were counselled for the use of an IUD as their choice of contraception. Potential women were asked for their interest to participate in the study and written informed consent were obtained by the medically qualified person after explaining about the device, its use and alternative methods of contraception. Pre-enrolment assessment for her healthy being pertaining to general, systemic, menstrual and psychosexual health with her fitness to use contraception were conducted.

The device :

The Fiona is a T-shaped low-density polyethylene device with each vertical and horizontal arm of 32 mm (Fig 1a). The low-density polyethylene of T-frame is compounded with the radiopaque barium sulfate which makes it easily visible on X-ray. There is a brown monofilament polyethylene removal thread tied at the base of the vertical arm for identification and removal of the device. Iron oxide is used as a colorant in the polyethylene removal thread. The active ingredient, LNG, is dispersed in a silicone reservoir on the vertical stem of the device. This reservoir containing 52 mg of LNG is covered by a semi-opaque polydimethylsiloxane membrane which allows controlled release of LNG at the rate of 20 µg/day over a period of 5 years. The release of LNG gradually decreases after five years of use. Currently Fiona LNG-IUD is approved for sale in India.

Device insertion :

The device placement was performed by healthcare professionals using aseptic techniques according to instruction for use. A bimanual examination was performed before the insertion procedure. Vagina and cervix were cleansed with the suitable antiseptic solution. Gentle traction was applied after grasping the upper lip of cervix with a tenaculum forceps to align the cervical canal with uterine cavity. The uterine sound was performed to measure the depth and check the direction of the uterine cavity. In case of a retroverted uterus, traction was applied on the lower cervical lip. The uterine sound of 6 to 10 cm was considered safe for IUD insertion. Use of dilatation was advised if cervical stenosis was encountered. The insertion technique of LNG-IUD in uterine cavity is depicted in Fig 1b.

Pharmacokinetic analysis :

In a subset of 27 women, blood samples (each of 5 mL) were drawn at different time intervals through indwelling intravenous cannulation. The blood samples were taken at 1-, 6-, and 12-month intervals. Blood samples were

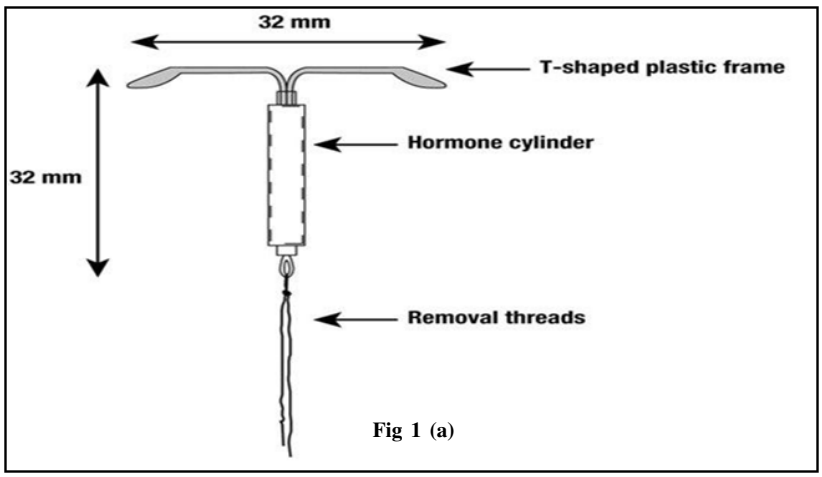

Fig 1 (a)

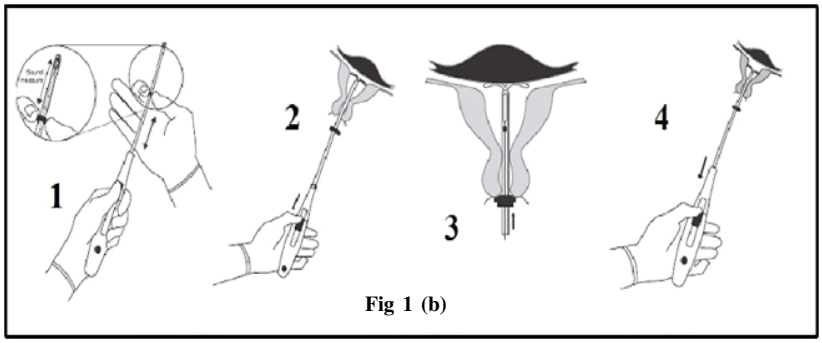

Fig 1 (b)

Fig 1 : (a) The levonorgestrel-releasing intrauterine system. (b) Simplified insertion procedure of the Fiona LNG-IUD; Step 1: After completion of sound measurement of uterine depth, adjust the depth by pushing the switch in forwarding direction. Step 2: The device is pushed into the uterine cavity and pulls the switch to open horizontal arms of Fiona. Step 3: Push inserted tube into the uterine cavity up to the fundus till flange touches to cervix. Step 4: To release Fiona, pull down switch and the thread is trimmed. Proper placement of Fiona in uterine cavity is assessed by ultrasound/X-ray examination.

anticoagulated with dipotassium ethylenediaminetetra acetic acid and centrifuged at 3000 ± 100 RCF for 5 minutes at room temperature to separate plasma. These separated plasma samples were stored at ≤20°C until analysis. The plasma samples were examined at Lambda Therapeutic Research Ltd, Ahmedabad, India. Plasma concentration of LNG was analyzed using liquid chromatography-tandem mass spectrometry method with the lower limit of quantification of 20.0 pg/mL and the upper limit of quantification of 15004.710 pg/mL. For calculation of pharmacokinetic parameters, the non-compartmental model was applied by using WinNonlin enterprise software version 5.3 (Pharsight Corporation, USA).

Study endpoints :

The primary endpoint was a failure of contraception defined as an occurrence of intra-uterine or ectopic pregnancy in the presence of study device or due to auto-expulsion of study device. Safety endpoints included; number of women with intra- and postprocedural perforation of uterus; number of women presented one or more conditions like significant endometrium injury, myometrium injury, PID, severe leucorrhoea or endometritis not relieved by medical intervention and required removal of device as well as expulsion or partial expulsion of the device.

At the baseline visit, demographics, vitals, physical examination, gynecological and medical history, hematology, previously used contraceptive method, urine pregnancy test (UTP), HIV, VDRL, and Papanicolaou test were performed. Scheduled clinical FUs were at 1 month (±10 days), 3 months (±15 days), 6 months (±30 days), and 12 months (±30 days) after LNG-IUD insertion and after that yearly (±30 days) for five years. AEs were recorded at each visit. The menstrual (inter-menstrual bleeding/spotting, dysmenorrhea, missed periods, vaginal discharge) and symptomatic (abdominal/back pain, headache, mood changes, acne or other skin/hair problems, breast tenderness, edema, weight gain) questionnaires were recorded at each FU.

Statistical analysis :

Descriptive statistics were performed for all variables; continuous variables were summarized by the mean ± standard deviation and categorical data was presented as frequency and percentage. Kaplan-Meier survival function was used to estimate the continuation rates for the LNG-IUD at 12 months after insertion. The analysis was performed using Statistical Package for Social Sciences, version 20 (Chicago, IL, USA). This was a non-comparative, prospective, post-marketing surveillance study. So there was no formal hypothesis testing and power calculation performed. We arbitrarily enrolled 309 women from theoretical predictions to draw the performance and safety pattern of the Fiona LNG-IUD.

Observations

Out of 318 women screened for the study, a total of 309 women (31.02 ± 4.90 years), were enrolled. Table 1 depicts baseline characteristics of the enrolled women. The device was successfully implanted in all women except one who suffered from a minor complication due to the tightness of cervical canal. Safety and clinical performance of an LNG-IUD in 306 women at 1-month, 301 women at 3-month, 295 women at 6-month and 294 women at 12-month FU are presented in this study. The detail of study disposition is represented in Fig 2.

Table 1 — *Demographics and baseline clinical characteristics of study population*

Demographics	Fiona LNG-IUD (N=309)
Age, years, mean ± SD	31.02 ± 4.90
19-30 years (%)	142 (45.9%)
31-40 years (%)	167 (54.0%)
Body mass index, kg/m^2, mean ± SD	24.1± 4.2
Marital Status, n (%) :	
Married	309 (100%)
Parity, n (%) :	
Parous	309 (100%)
One live birth	182 (58.90%)
Two	107 (34.63%)
Three or more live births	20 (6.47%)
Gynecological and obstetric history, days :	
Bleeding duration, mean ± SD	4.7± 0.9
Menstrual interval, mean ± SD	28.7± 2.7
Previous contraceptive use, n (%) :	
Barrier contraceptive	23 (7.4%)
Oral contraceptive	109 (35.3%)
Copper IUD	64 (20.7%)
Mechanical contraceptive	22 (7.1%)
None	91 (29.4%)

SD, standard deviation; IUD, intrauterine device

In the present study, no intra-uterine or ectopic pregnancy was reported till 12-month. None of the women reported intra-procedural or post-procedural uterus perforation, endometrium or myometrium injury, PID, severe leucorrhoea or endometritis and expulsion or partial expulsion. Besides these, there was no safety concern reported in 294 patients till 12-month.

The LNG release from Fiona is 20 µg/day directly get delivered into the uterine cavity. A mean plasma LNG concentrations of 275.08±104.03 pg/mL at 1-month (n=27) and 227±84 pg/mL at 6-month (n=23) have been reported in this study. The results of mean plasma LNG concentrations at the remaining FU will be reported in the upcoming report.

The continuation rate at 12-month for the Fiona LNG-IUD was 95.47 % is demonstrated by Kaplan-Meier curve (Fig 3). Fourteen women (4.53%) were reported to have discontinued use of Fiona LNG-IUD at 12-month; among which 13 had discontinued before 6-month of study duration. Out of 14, 12 (3.9%) women discontinued the study due to AE, and other two women (0.65%) had withdrawn consent due to personal reasons. There were multiple reasons reported for the discontinuation, as listed in Table 2. Bleeding-related reasons (n=6) and abdominal pain (n=4) were mentioned more frequently by women who were discontinuing the study. One woman requested removal of LNG-IUD due to constant spotting for 25 days after device implantation; whereas one woman felt discomfort with device and weight gain after implantation which resulted in LNG-IUD removal.

None of the women reported serious adverse event associated with Fiona LNG-IUD in the present study. However, a total of 30 AEs occurred in 21 women till 12-month FU. These AE included bleeding problems (11/30), abdominal pain (6/30), spotting (5/30), pelvic pain (2/30), weight gain (2/30), body pain (1/30), lower abdominal discomfort (1/30), nausea (1/30) and discomfort due study device (1/30). The cumulative AEs at each FU till 12 months are summarized in Table 3.

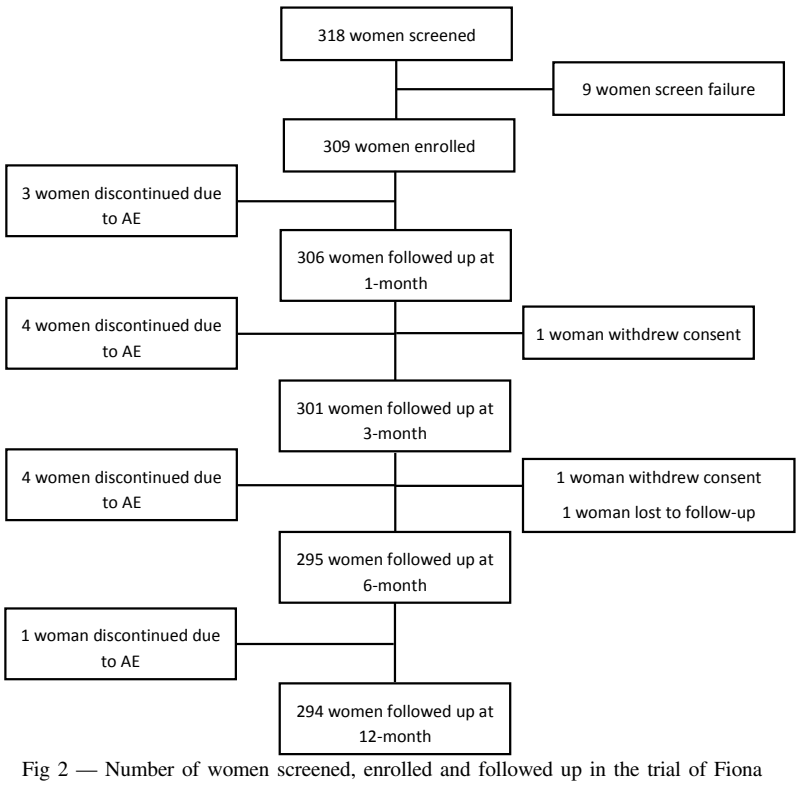

Fig 2 — Number of women screened, enrolled and followed up in the trial of Fiona LNG-IUD; AE : Adverse event

Discussion

The study was planned to demonstrate the performance and safety of Fiona LNG-IUD for contraceptive use. The contraceptive performance of the device up to 12-month was established based on contraception failure which was not reported in the 294 studied women. Although 30 AEs were documented till 12-month FU; however, none of the enrolled women experienced uterine perforation, endometrium or myometrium injury, expulsions or any other complication up to 12-month FU.

Contraception is the primary indication of Fiona LNG-IUD. The insertion technique

Table 2 — *Listing of women who discontinued treatment with LNG-IUD during the study*

Age (years)	Time of discontinuation (months)	Reasons for removal
39	0.2	Bleeding
36	0.2	On-and-off lower abdominal pain, relieved by medications
35	0.9	Spotting
28	1.7	Bleeding
31	1.7	Bleeding
29	2	Constant bleeding after device insertion
39	2.5	Constant bleeding after device insertion
36	2.5	Subject Withdraw Consent due to personal reason
31	4.7	Bleeding
30	4.7	Lower abdominal pain, not resolved by medications
32	5.6	weight gain, uncomfortable with device
36	5.7	Lower Abdominal Pain not relieved by medications
31	5.9	Subject Withdraw Consent due to personal reason
33	11.4	Moderate abdominal pain, not resolved by medications

of Fiona is simple and can be easily performed by health care professional with least training required. The presence of descending transverse arms serves to protect against unintentional perforation of the uterus during insertion. The primary mechanism of action of LNG-IUD targets the endometrium by releasing LNG into the uterine cavity. The high local LNG concentration thickens cervical mucus, makes the endometrium thin and decidualized, and also produces an unsuitable environment for sperm survival and fertilization, which represents a key mechanism of contraceptive action of LNG-IUD[9].

The performance of Fiona LNG-IUD was determined by the failure of contraception (occurrence of intra-uterine or ectopic pregnancy) in the present study. In 1-year FU survey, the pregnancy rate was significantly lower for 52-mg LNG-IUD compared to different copper-IUDs10. Previously reported ectopic pregnancy rates for LNG-IUD users ranged from 0.02% to 0.2% at 12-month[10]. However, several studies have reported no pregnancy during use of the LNG-IUD for over a period of 5 years[11-13]. Likewise, our study does not report any ectopic or intra-uterine pregnancy which depicts good performance of LNG-IUD till 12-month.

Low uterine perforation rate at the time of insertion (1.4/1000 insertions) was reported in EURAS IUD study[14]. ACCESS IUS study at 3-year FU reported 0.17% uterine perforation rate as well as 3.5% expulsion rate; most expulsions (80.6%) occurred in the first year of product use[15]. However, there wasn't any perforation of the uterus or expulsion of study device reported in the present study at 12-month, which demonstrates good safety profile of the study device. Several previous studies reported PID incidence ranging from 0.1% to 1.9% in the months following insertion[16,17]. In the present study, there was no incidence of pelvic infection following insertion.

One-year continuation rates for standard intrauterine device (IUD) initiation in previously published studies ranged from 80% to 88% for 52 mg LNG-IUD[18,19]. It was observed that most of the women discontinued the use of IUD as a consequence of bleeding and pain[19-21]. The similar results were observed in the present study as 6 out of 12 women reported bleeding problems and 4 out of 12 women complained abdominal pain as a reason for their discontinuation. Frequency and irregularity of bleeding are common changes in the majority of women during the first few months after insertion of the LNG-IUD[20,22]. However, the pattern of both bleeding and spotting decrease considerably after prolonged use of LNG-IUD in above-mentioned studies. In the present study, most AEs were reported at 3- and 6-month after LNG-IUD implantation and the occurrence of AE considerably decreased at 12-month FU.

Nevertheless, LNG-IUDs are meant to act locally at the uterine cavity; low level of LNG is absorbed into systemic circulation swiftly. It was observed that maximum plasma LNG level reached after few hours of insertion and the plateau of 150-200 pg/mL after the few weeks of insertion

Table 3 — *Cumulative adverse events*

Type of adverse event	In hospital (N=309)	1-month FU (N=306)	3-month FU (N=301)	6-month FU (N=295)	12-month FU (N=294)
Bleeding problems	0	5	10	11	11
Pelvic pain	0	0	1	2	2
Spotting	0	2	3	5	5
Abdominal pain	0	2	2	5	6
Ache/Body pain	0	1	1	1	1
Lower abdominal discomfort	0	0	1	1	1
Nausea	0	0	1	1	1
Weight gain	0	0	1	2	2
Uncomfortable with study device	0	0	0	1	1
Cumulative events, n (%)	0	10	20	29	30

FU: Follow-up

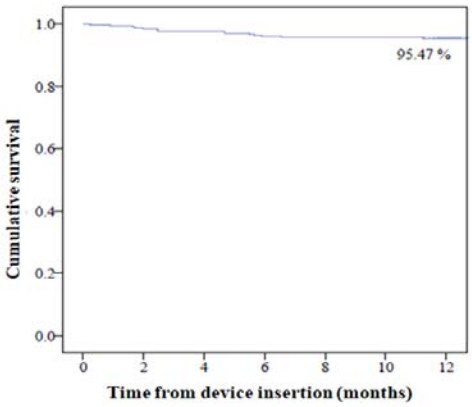

Fig 3 — Kaplan–Meier survival curve of IUD continuation

was reported for Mirena LNG-IUD[23]. LNG concentrations after short-term use of Fiona at 1-month (275.08±104.03 pg/mL) and 6-month (227±84 pg/mL) appeared parallel (p=0.11) to the 6-month (n=36) LNG concentration 195±68 pg/mL of an LNG-IUD LILETTA[24]. This shows an admissible pharmacokinetic profile of the study device.

Large sample size would have provided more insights into the usage of LNG-IUD and its safety and performance in Indian women, especially in relation to events such as expulsions of device and safety. Notwithstanding these limitations, the study will provide factual findings of pharmacokinetic profile, safety, and performance of LNG-IUD at 5 years, which could be constructive for future investigations in Indian women.

In conclusion, Fiona LNG-IUD showed favorable safety profile and good performance in most of the Indian women who remained in the study at 12-month. The claim of long-term contraception of Fiona LNG-IUD is to be assessed from future results of 5-year FU.

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Conflict of interest :

Dr Ashok Thakkar and Bhavi Patel are full-time employee of Meril Life Sciences Pvt Ltd, India. The other authors declare no conflicts of interest.

References

1 Costescu DJ — Levonorgestrel-releasing intrauterine systems for long-acting contraception: current perspectives, safety, and patient counseling. *Int J Womens Health* 2016; **8:** 589-98.
2 Kailasam C, Cahill D — Review of the safety, efficacy and patient acceptability of the levonorgestrel-releasing intrauterine system. *Patient Prefer Adherence* 2008; **2:** 293-302.
3 Singh S, Shekhar C, Acharya R, Moore AM, Stillman M, Pradhan MR, *et al* — The incidence of abortion and unintended pregnancy in India, 2015. *The Lancet Global Health* 2018; **6(1):** e111-e20.
4 Buhling KJ, Zite NB, Lotke P, Black K — Worldwide use of intrauterine contraception: a review. *Contraception* 2014; **89(3):** 162-73.
5 Sheet IF — NFHS-4 (National Family Health Survey-4). International Institute for Population Studies. 2017.
6 Kriplani A, Singh B, Lal S, Agarwal N — Efficacy, acceptability and side effects of the levonorgestrel intrauterine system for menorrhagia. *International Journal of Gynecology & Obstetrics* 2007; **97(3):** 190-4.
7 Gopimohan R, Chandran A, Jacob J, Bhaskar S, Aravindhakshan R, Aprem AS — A clinical study assessing the efficacy of a new variant of the levonorgestrel intrauterine system for abnormal uterine bleeding. *International Journal of Gynecology & Obstetrics* 2015; **129(2):** 114-7.
8 Kriplani A, Awasthi D, Kulshrestha V, Agarwal N — Efficacy of the levonorgestrel-releasing intrauterine system in uterine leiomyoma. *International Journal of Gynecology & Obstetrics* 2012; **116(1):** 35-8.
9 Group ECW — Intrauterine devices and intrauterine systems. *Human Reproduction Update* 2008; **14(3):** 197-208.
10 Heinemann K, Reed S, Moehner S, Minh TD — Comparative contraceptive effectiveness of levonorgestrel-releasing and copper intrauterine devices: the European Active Surveillance Study for Intrauterine Devices. *Contraception* 2015; **91(4):** 280-3.
11 Faúndes A, Alvarez F, Díaz J — A Latin American experience with levonorgestrel IUD. *Annals of medicine* 1993; **25(2):** 149-53.
12 Hidalgo MM, Hidalgo-Regina C, Bahamondes MV, Monteiro I, Petta CA, Bahamondes L — Serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel-releasing intrauterine system. *Contraception* 2009; **80(1):** 84-9.
13 Bahamondes L, Fernandes A, Bahamondes MV, Juliato CT, Ali M, Monteiro I — Pregnancy outcomes associated with extended use of the 52-mg 20 µg/day levonorgestrel-releasing intrauterine system beyond 60 months: A chart review of 776 women in Brazil. *Contraception* 2018; **97(3):** 205-9.
14 Heinemann K, Reed S, Moehner S, Minh TD — Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices. *Contraception* 2015; **91(4):** 274-9.
15 Eisenberg DL, Schreiber CA, Turok DK, Teal SB, Westhoff CL, Creinin MD, *et al* — Three-year efficacy and safety of a new 52-mg levonorgestrel-releasing intrauterine system. *Contraception* 2015; **92(1):** 10-6.
16 Steen R, Shapiro K — Intrauterine contraceptive devices and risk of pelvic inflammatory disease: standard of care in high STI prevalence settings. *Reproductive Health Matters* 2004; **12:** 136-43.
17 Sufrin CB, Postlethwaite D, Armstrong MA, Merchant M, Wendt JM, Steinauer JE — Neisseria gonorrhea and Chlamydia trachomatis screening at intrauterine device insertion and pelvic inflammatory disease. *Obstetrics & Gynecology* 2012; **120(6):** 1314-21.
18 Sanders JN, Turok DK, Royer PA, Thompson IS, Gawron LM, Storck KE — One-year continuation of copper or levonorgestrel intrauterine devices initiated at the time of emergency contraception. *Contraception* 2017; **96(2):** 99-105.
19 Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I — Clinical performance of a levonorgestrel-releasing intrauterine system and oral contraceptives in young nulliparous women: a comparative study. *Contraception* 2004; **69(5):** 407-12.
20 Andersson K, Odlind V, Rybo G — Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception* 1994; **49(1):** 56-72.
21 Luukkainen T, Allonen H, Haukkamaa M, Holma P, Pyörälä T, Terho J, *et al* — Effective contraception with the levonorgestrel-releasing intrauterine device: 12-month report of a European multicenter study. *Contraception* 1987; **36(2):** 169-79.
22 Suvisaari J, Lähteenmäki P — Detailed analysis of menstrual bleeding patterns after postmenstrual and postabortal insertion of a copper IUD or a levonorgestrel-releasing intrauterine system. Contraception 1996; **54(4):** 201-8.
23 Nelson AL, Massoudi N — New developments in intrauterine device use: focus on the US. *Open access journal of contraception* 2016; **7:** 127-41.
24 USFDA — Highlight of prescribing information for Liletta (TM). 2015.