

## COMMENTARY

# Thirty years of mirena: A story of innovation and change in women's healthcare

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## Abstract

Since its introduction in 1990, the levonorgestrel-releasing intrauterine system (LNG-IUS) has played a key role in shaping the healthcare landscape of women. Here we explore the development of the first LNG-IUS (Mirena®) and the early clinical trials that demonstrated its potential. We highlight the contraceptive and therapeutic benefits of Mirena®, and discuss how clinical practice has been changed since the introduction of LNG-IUS and other long-acting reversible contraceptive methods. The history of Mirena® is rich in innovation and has also paved the way to the development of smaller intrauterine systems with lower hormone doses. Along with Mirena®, these newer LNG-IUS contribute to improving contraceptive choices for women, allowing them to select the option that is right for them and that meets their needs no matter their age, parity or circumstances.

## KEYWORDS

contraception, levonorgestrel-releasing intrauterine system, intrauterine device, women's health issues

## 1 | INTRODUCTION

Sexual and reproductive health constitute fundamental human rights and play a vital role in the empowerment of women and achievement of gender equality; ensuring universal access to sexual and reproductive health services is essential to achieving this goal.<sup>1</sup> Worldwide, around 40% of pregnancies are unintended,<sup>2</sup> with considerable negative consequences for the woman, her existing children and her family as well as an economic burden on the affected individuals and society.<sup>3,4</sup>

The provision of quality reproductive health services and education, access to family planning and postpartum contraception, as well

as safe abortion services and post-abortion care, are important to empower women, helping them to achieve their goals and ambitions, avoid unwanted pregnancy and ensure any pregnancy occurs at the right time for them. The introduction of the first oral contraceptive pill in 1960 sparked a movement to put women in control of their sexual and reproductive health through the use of effective modern methods of contraception. Since then, as attitudes have shifted and technology has advanced, a wide variety of contraceptive methods have become available, enabling women to choose a method that is right for them in different reproductive life phases.

Long-acting reversible contraceptives, which include the implant and both hormonal and non-hormonal intrauterine devices (IUDs),

**Abbreviations:** Cu-IUD, copper intrauterine device; HMB, heavy menstrual bleeding; IUD, intrauterine device; IUS, intrauterine system; LNG-IUS, levonorgestrel-releasing intrauterine system.

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are highly effective and acceptable options requiring minimal routine follow-up or prescription renewal. Intrauterine contraception is used by around 160 million women worldwide, accounting for about 14% of all contraceptive users.<sup>5</sup>

The first intrauterine contraceptives were mainly non-medicated, “plastic” IUDs that had been available since 1968 but are no longer on the market.<sup>6</sup> Copper IUDs (Cu-IUDs) were subsequently introduced, followed by progestin-releasing devices. Mirena® (Bayer AG), a levonorgestrel-releasing intrauterine system (LNG-IUS), was the first levonorgestrel-releasing intrauterine contraceptive to be introduced to the market. It was first launched 30 years ago in Finland in 1990 and is now available in over 120 countries worldwide.<sup>7</sup>

## 2 | RIGHT PLACE, RIGHT TIME, THE ELEMENTS THAT CAME TOGETHER TO FACILITATE THE DEVELOPMENT OF MIRENA®

A number of technological developments and advances in the understanding of hormones between the 1930s and 1950s made the first steps toward a hormonal intrauterine system (IUS) possible; understanding of the effects of steroid hormones was advanced, progesterone was characterized and the first synthetic progestins (norethindrone/norethisterone) were developed.<sup>8</sup> Furthermore, materials such as polydimethylsiloxane were developed that allowed for the controlled release of drug substances over an extended period of time.<sup>9</sup>

Progestin-containing IUSs were originally developed to reduce some of the adverse events associated with Cu-IUDs, such as heavy and/or prolonged bleeding, dysmenorrhea and expulsion.<sup>6,10</sup> The first progestin-containing IUS with sustained release demonstrated promising results: there were no unintended pregnancies, no systemic effects and no impact on ovarian function.<sup>11</sup> Between 1974 and 1976, additional small studies on progestin-containing IUSs demonstrated low pregnancy rates, reductions in bleeding and low systemic exposures; however, expulsion rates were high owing to the early spiral-frame designs.<sup>11-13</sup> Building on this, the research team headed by Professor Tapani Luukkainen from the University of Helsinki, a member of the Population Council and the International Committee for Contraception Research, pioneered the development of an IUS with a T-shaped frame that released a progestin then called d-norgestrel (ie levonorgestrel). In 1977, a pilot study of a d-norgestrel-releasing IUS with polydimethylsiloxane coating on the drug reservoir and a T-shaped frame was conducted. This demonstrated steady release of d-norgestrel in the intrauterine cavity, with reductions in menstrual blood loss, uniform endometrial suppression and a favorable safety profile.<sup>14</sup>

## 3 | MIRENA®: CONTRACEPTIVE EFFICACY, SAFETY AND ACCEPTABILITY

The first four clinical trials involving Mirena® took place between 1985 and 1994 (it should be noted that the product was initially

### Key message

Mirena® was the first levonorgestrel-releasing intrauterine system (LNG-IUS) introduced. Its contraceptive and therapeutic benefits shaped women’s healthcare and paved the way for other LNG-IUS, offering more contraceptive choices and making management of common gynecological conditions safer and more cost-effective.

named Levonova, and later marketed as Mirena®). A randomized comparative trial carried out in 1985 on two LNG-IUSs vs a Cu-IUD found that at 5 years, the LNG-IUSs had a Pearl Index of 0.11, demonstrating the minimum effective lifespan of the devices.<sup>10</sup> In 1989, a comparative clinical trial of a T-frame LNG-IUS vs three different Cu-IUDs observed no pregnancies with LNG-IUS and high continuation rates at 1 year.<sup>15</sup> Two international, multicenter studies carried out in 1990 and 1994 demonstrated a 5-year cumulative pregnancy rate of 0.5%-1.1% for Mirena® compared with 1.4%-5.9% for Cu-IUD.<sup>16,17</sup> Together, these trials demonstrated that Mirena® provides highly effective contraception for up to 5 years. Mirena® was additionally approved for 6 years of use by the U.S. Food and Drug Administration in August 2020.

Since its introduction, Mirena® has been studied in a variety of clinical and observational studies that have further demonstrated efficacy, safety, tolerability and acceptability in parous, young and nulliparous women.<sup>18,19</sup> LNG-IUS is associated with a significantly lower risk of pregnancy, including ectopic pregnancy, compared with the Cu-IUD.<sup>20</sup>

Furthermore, placement in both parous and nulliparous women is considered easy by the majority of healthcare professionals and placement associated with no more than mild/moderate pain in most women.<sup>18</sup> Continuation with Mirena® is high overall, with continuation rates of over 90% at 1 year.<sup>21</sup> Satisfaction is also high, with one recent study demonstrating that 92.5% of women using their Mirena® for 6 years were very satisfied with the device.<sup>22</sup> Satisfaction and continuation rates are consistent with other long-acting contraceptive methods including other LNG-IUS.<sup>6,19,23</sup>

Users of Mirena® may experience adverse events typical of hormonal contraception, such as abdominal pain, headache, breast tenderness and acne, and in some instances these may lead to discontinuation.<sup>17,18</sup> In addition, changes in menstrual bleeding pattern are common in the initial months following placement, with the potential for irregular bleeding and spotting owing to the local effects of LNG on the endometrium.<sup>17,19</sup> It is important that healthcare providers include information on potential bleeding pattern changes and side-effects when counseling women about LNG-IUS, as this can help manage expectations and contribute to improved continuation.<sup>21</sup> Other adverse events such as ovarian cysts and uterine perforation can also occur, though these are rare.<sup>17,23</sup>

## 4 | BENEFITS OF MIRENA® BEYOND CONTRACEPTION

### 4.1 | Mirena® impacts on menstrual bleeding profile

Ever since the first clinical trials, it has been noted that a large proportion of women using Mirena® will experience a decrease in menstrual bleeding over time.<sup>19</sup> Furthermore, women who have a second Mirena® placement do not experience the short-term bleeding irregularities commonly seen after placement of the first device.<sup>24</sup> Some women may experience amenorrhea, and in early trials up to 20% discontinued because of this,<sup>16,17</sup> however, many women now consider amenorrhea a positive effect and it has been associated with high satisfaction rates<sup>24</sup> as well as imparting several health benefits.

### 4.2 | Providing relief from the burden of heavy menstrual bleeding

Heavy menstrual bleeding (HMB) is the most common presentation of abnormal uterine bleeding and affects up to 30% of women at some point in their life.<sup>25,26</sup> HMB can be defined as excessive menstrual blood loss (>80 mL per cycle) that interferes with a woman's physical, emotional, social and material quality of life.<sup>25-28</sup>

HMB may be attributed to a variety of causes including structural and non-structural pathologies that can be classified according to the PALM-COEIN algorithm.<sup>26</sup> Mirena® is licensed for the treatment of "idiopathic menorrhagia". The term "idiopathic menorrhagia" has been replaced with the terminology "HMB without identified underlying pathology", which is more readily understood by both women and healthcare providers. Although only licensed for the treatment of HMB without an identifiable cause, Mirena® has also demonstrated efficacy in reducing menstrual blood loss in women with HMB associated with underlying structural pathologies such as adenomyosis and leiomyomas.<sup>29,30</sup> It is important to note, however, that these indications are off-label.

Mirena® is recommended as a first-line treatment option for HMB by several international guidelines,<sup>28,31,32</sup> and demonstrates a rapid, significant and clinically meaningful reduction in menstrual blood loss over time and subsequent improvements in hemoglobin and ferritin levels.<sup>33,34</sup> It also offers an effective alternative to endometrial ablation, transcervical resection and hysterectomy for the treatment of HMB and can be used in younger women with a desire to preserve fertility.<sup>34</sup>

### 4.3 | Managing menstrual symptoms in young women

Dysmenorrhea is the most commonly reported gynecological condition among adolescents and young women, with a significant impact on quality of life, mood, sleep quality and productivity during

menstruation.<sup>35</sup> Mirena® is effective in alleviating dysmenorrhea in a large proportion of women, including dysmenorrhea associated with endometriosis.<sup>18,23</sup> It also recommended in guidelines as an effective first-line treatment for adolescents with dysmenorrhea that is resistant to oral therapy.<sup>36,37</sup>

### 4.4 | Providing reassurance of endometrial protection while taking menopausal hormone therapy

Mirena® may be particularly suited for perimenopausal women who, due to increasing anovulatory cycles (and possible consequent endometrial hyperplasia), may be more likely to experience bleeding disturbances including HMB.<sup>38,39</sup>

Menopausal hormone therapy with estrogen is a well-established method of managing symptoms such as hot flashes, sleep disturbances, mood changes and diaphoresis in women approaching the menopause but is associated with a significant risk of endometrial hyperplasia if not counterbalanced with concomitant progestogen administration.<sup>39</sup> The endometrial suppression caused by Mirena® protects against estrogen-induced endometrial hyperplasia during menopausal hormone therapy in peri- and postmenopausal women, allowing women to safely continue their treatment to reduce climacteric symptoms.<sup>39</sup>

### 4.5 | Changing women's healthcare landscape

One of the trends noticed since the introduction of LNG-IUS is the increased use of long-acting reversible contraceptives with subsequent reduction in unintended pregnancy and abortion.<sup>40</sup> A recent study in Finland found that a comprehensive service, which provided both termination of pregnancy and provision of intrauterine contraception, resulted in increased rates of attendance and IUS use, as well as a significantly lower risk of subsequent abortion.<sup>41</sup>

The increasing popularity and recommendation of long-acting reversible contraceptives has also seen a subsequent decrease in the number of surgical sterilization procedures being carried out.<sup>42</sup> Furthermore, introduction of guidance using medical management as first-line treatment of HMB has been associated with reduction in hysterectomy in several countries.<sup>43</sup> Around 30% of hysterectomies are performed to alleviate HMB; however, current gynecological practice favors more conservative medical treatment where possible. By providing effective treatment for HMB, LNG-IUS such as Mirena® offer an alternative to hysterectomy for women, particularly those who wish to preserve their fertility.

## 5 | LOOKING TO THE FUTURE

Progress in the healthcare landscape of women does not stop with LNG-IUS. The field continues to expand with new developments and ways to improve contraceptive counseling, choice for women and

ensure that women have positive experiences with the method they have chosen.

With regards to LNG-IUS in particular, real-world evidence generated from studies of thousands of women continues to enhance understanding of how LNG-IUS perform in the real world,<sup>19-21</sup> and further clinical studies offer the potential to extend or expand the use of already available LNG-IUS options.<sup>22</sup> Furthermore, next-generation intrauterine contraceptives are being investigated. Although the popularity of long-acting reversible contraceptives, and intrauterine contraceptives in particular, has increased substantially, with high acceptability among women, use of these effective methods still remains below that of other less-effective contraceptives. This is thought to result from several factors that might include misperceptions or lack of knowledge of IUS among women and healthcare providers, lack of awareness of benefits as well as fear of potential alterations in hormone levels or bleeding patterns and the adverse consequences these may bring.<sup>44-46</sup> The history that started with Mirena® may be the basis for the development of new devices with targeted delivery of therapeutic and contraceptive agents that further improve aspects such as the post-insertion bleeding profile, further enhancing women's experience with IUSs.

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#### CONFLICT OF INTEREST

Kristina Gemzell-Danielsson has been ad hoc advisory board member or invited to give presentations for Merck (MSD), Bayer, Exelgyn, Actavis, Gedeon Richter, Mithra, Exeltis, Ferring, Natural Cycles, Azanta, Gynuity, Campus Pharma, and HRA-Pharma. Oskari Heikinheimo serves occasionally on advisory boards for Bayer AG, Gedeon Richter, Sandoz and Vifor Pharma, and has lectured at educational events organized by these companies. Ali Kubba has taken part in sponsored educational activity and served on advisory boards for pharmaceutical companies including Bayer, Merck and Exeltis. Thomas Faustmann is an employee of Bayer AG, Berlin, Germany. Cecilia Caetano is an employee of Bayer Consumer Care AG, Basel, Switzerland. Eeva Lukkari-Lax is an employee of Bayer OY, Espoo, Finland.

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