Over 20 million women worldwide have selected Mirena®

Mirena® is a unique levonorgestrel-releasing intrauterine system that provides high contraceptive reliability – Mirena® in situ almost never fails. It is so effective as a contraceptive that it competes with female sterilization, but with the advantage of complete reversibility following removal. Women considering sterilization should be counseled about the use of long-term reversible contraception such as Mirena® so as to avoid any regret associated with permanent loss of fertility. Moreover, there is a rapid return to ‘normal’ fertility following the removal of Mirena®.

In addition to the main indication as a contraceptive, the local release of levonorgestrel by Mirena® into the uterine cavity results in profound changes in the endometrium: the glands of the endometrium atrophy, the stroma becomes swollen and decidual, the mucosa thins and the epithelium becomes inactive. Through this inactivation of the endometrium, Mirena® is able to provide a range of other benefits such as the alleviation of menorrhagia and protection against endometrial hyperplasia in women receiving estrogen replacement therapy (ERT).

Consequently, Mirena® reduces menstrual blood loss, resulting in shorter, lighter and less painful periods; or, in the case of ERT, Mirena® does not reintroduce the regular cyclical bleeding associated with sequential hormone replacement therapy. In women with menorrhagia, menstrual bleeding is reduced by more than 80%, leading to a significant increase in the levels of hemoglobin and serum ferritin. Amenorrhea is frequently reported but, because there is no hypoestrogenism, this is a benefit. Moreover, Mirena® is the most effective medical therapy for the treatment of menorrhagia and its use provides an effective alternative to endometrial ablation or hysterectomy. Unlike the latter treatments, however, Mirena® does not compromise future fertility.

Irregular spotting and bleeding may be common problems in the first few weeks or months after the insertion of Mirena®, and all prospective users should be forewarned of this. Adequate counseling helps women to understand such changes and accept them as more of a nuisance than a health threat. Indeed, such counseling at the time of insertion is strongly associated with increased user satisfaction. In general, the high continuation rates observed with Mirena® in both users of contraceptive and hormone replacement therapy attest to its good tolerability and acceptability.

In short, in my opinion, Mirena® remains a significant advance in reversible contraception since ‘the Pill’.

John Guillebaud

Professor Emeritus of Family Planning and Reproductive Health Department of Obstetrics and Gynaecology
University College London Medical School, London, UK
1. Mirena® in brief

**KEY POINTS:**

- Mirena® is a long-acting, hormone-releasing intrauterine contraceptive system
- Mirena® provides high contraceptive reliability with lighter, shorter, and less painful periods
- Mirena® reduces menstrual blood loss in women with menorrhagia and improves hemoglobin and body iron stores
- Mirena® is an effective alternative to hysterectomy in the treatment of menorrhagia and is associated with significantly fewer costs
- Mirena® effectively prevents endometrial hyperplasia during estrogen replacement therapy (ERT)
- Appropriate counseling before insertion of Mirena® results in high continuation rates and user satisfaction
What is Mirena®?

Mirena® is a long-acting intrauterine hormone-releasing contraceptive system. It comprises a small flexible plastic T-shaped frame (length: 32 mm) bearing a levonorgestrel (LNG)-containing cylinder. After insertion into the uterus, LNG is released from the cylinder in small doses (initial release rate, 20 μg/day) into the uterine cavity. Mirena® provides effective contraception with lighter, shorter and less painful periods.1–5

How does Mirena® work?

The contraceptive and therapeutic effects of Mirena® are mainly based on three local effects of LNG in the uterus:

- thickening of the cervical mucus6,7
- inhibition of sperm motility and function inside the uterus and the fallopian tubes, preventing fertilization8,9
- prevention of endometrial growth10,11

What are the benefits of Mirena®?

Based on these mechanisms, Mirena® provides high contraceptive reliability: the failure rate of Mirena® is approximately 0.2% at 1 year and a cumulative failure rate of approximately 0.7% at 5 years.12 This contraceptive efficacy is comparable to that of female sterilization, with full reversibility of fertility upon removal. Moreover, the ectopic pregnancy rate with Mirena® is approximately 0.1% per year,12 which is much lower than the estimated rate for women not using any contraception (0.3–0.5% per year).13

In addition to its contraceptive action, Mirena® also leads to a significant reduction in both the amount and duration of menstrual bleeding, and alleviates menorrhagia and dysmenorrhea. As a consequence, women using Mirena® show an increase in blood hemoglobin and serum ferritin levels, indicating a recovery of iron stores. The efficacy of Mirena® in the treatment of menorrhagia is comparable with endometrial ablation or resection,14–20 but unlike the latter treatments, does not compromise future fertility. Compared with hysterectomy, Mirena® achieves similar improvements in the quality of life of women with menorrhagia,21 but is less invasive than surgery and is associated with significantly fewer costs.22 The contraceptive efficacy and tolerability of Mirena® have been proved in everyday use: continuation rates at 1 and 5 years are 93% and 65%, respectively.23

Mirena® has also been shown to exert a strong, localized progestogenic effect on the endometrium that effectively prevents hyperplasia (the first step in the development of endometrial cancer) during ERT in peri- and post-menopausal women. In both contraceptive and therapeutic indications, side-effects, e.g. bleeding irregularities, are more common in the first few months following insertion, gradually diminishing with time. Providing appropriate counseling to prospective recipients of Mirena®, including information about efficacy, bleeding patterns and possible side-effects, may be expected to enhance the acceptability and continuation of use of the method.
2. Structure

KEY POINTS:

• Mirena® consists of a flexible plastic T-shaped frame

• The initial release rate of levonorgestrel (LNG) from Mirena® into the uterine cavity is 20 μg/day

• Mirena® is active for up to 5 years
2. Structure

Mirena® consists of a flexible plastic T-shaped frame with a steroid reservoir around the vertical stem (Figure 1). This reservoir consists of a cylinder, made of LNG and polydimethylsiloxane mixture, containing a total of 52 mg LNG (or 50% by weight). The reservoir forms a 19 mm-long ‘sleeve’ around the vertical arm of the plastic body and is covered by a polydimethylsiloxane membrane, which regulates the intrauterine release of LNG. The total length of the system is 32 mm.

Figure 1. Mirena® intrauterine hormonal system.

The T-shaped frame is impregnated with barium sulphate, which makes it radio-opaque, to enable detection by X-ray. A monofilament polyethylene removal thread is attached to a loop at the distal end of the T-frame. The system has a shelf-life of 3 years.

Mirena® is designed to fit easily in the uterus of women of reproductive age (Figure 2). The initial release rate of LNG into the uterine cavity is 20 μg/day, which declines to about 10 μg/day after 5 years.

The maximum duration of use for Mirena® in all indications is 5 years. Thereafter it should be removed and, if necessary, immediately replaced by a new system.

Figure 2. Ultrasound of Mirena® in situ. The arrows mark the ends of the vertical T-frame, with its dark shadow projecting downwards between them.
3. Mechanism of action

KEY POINTS:

• The contraceptive effects of Mirena® include a combination of thickening of the cervical mucus, inhibition of sperm motility/function and suppression of endometrial growth

• Mirena® makes the endometrium unresponsive to circulating estradiol (E2), irrespective of ovarian function, and through this endometrial suppression leads to less menstrual blood loss

• The potent endometrial suppression caused by Mirena® protects against estrogen-induced endometrial hyperplasia in hormone replacement therapy (HRT)
3. Contraception

The contraceptive effects of Mirena® are attributed to multiple mechanisms acting concomitantly:

- qualitative changes in the cervical mucus, making it impenetrable to sperm
- inhibition of sperm motility and function inside the uterus and the fallopian tubes, preventing fertilization
- prevention of endometrial growth

In some women ovulation is inhibited. A weak foreign-body reaction is also present.

The changes in cervical mucus/utero-tubal fluid, as well as the changes in endometrial morphology and ovarian function brought about by Mirena® contribute to the overall contraceptive effects. These studies have shown that thickening of cervical mucus and lack of sperm penetration is one of the principal mechanisms of contraceptive action of Mirena®. These contraceptive effects occur before conception and, as such, Mirena® cannot be regarded as an abortifacient.

3.1.1. Effects on cervical mucus and sperm function

Barbosa et al. suggested that cervical mucus production was reduced by Mirena® in some users, while Jonsson et al. reported an increase in the weight of cervical mucus, thus inhibiting the passage of sperm. Lewis et al. showed that the mid-cycle cervical mucus in women using Mirena® was poor quality and inhibits endocervical sperm transport. It has also been postulated that the migration of sperm through the uterine and fallopian tubal fluid is inhibited.

3.1.2. Endometrial effects

The high levonorgestrel (LNG) concentrations in the endometrium down-regulate endometrial estrogen and progesterone receptors, making the endometrium insensitive to circulating E2 (thereby suppressing endometrial growth). After only a couple of months of Mirena® use, the glands of the endometrium atrophy, the stroma becomes swollen and decidual, the mucosa thins and the epithelium becomes inactive – described by Perino et al. as ‘cylindrico-cubic, monolayered and without mitosis’. Vascular changes include a thickening of arterial walls, suppression of the spiral arterioles and capillary thrombosis. An inflammatory reaction characterized by an increase in neutrophils, lymphocytes, plasma cells and macrophages is described and focal stromal necrosis may also occur. The endometrial changes are uniform within 3 cycles after insertion of the system and no further histological development takes place over the long term. The endometrial morphological features associated with Mirena® use are summarized in Table 1.

<table>
<thead>
<tr>
<th>Morphological feature</th>
<th>Proportion of cases with feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decidualization of stroma</td>
<td>96%</td>
</tr>
<tr>
<td>Atrophy of glands</td>
<td>87%</td>
</tr>
<tr>
<td>Stromal inflammatory cell infiltrate</td>
<td>79%</td>
</tr>
<tr>
<td>Stromal inflammatory cell infiltrate including plasma cells</td>
<td>27%</td>
</tr>
<tr>
<td>Surface papillary formations</td>
<td>51%</td>
</tr>
<tr>
<td>Stromal myxoid change</td>
<td>39%</td>
</tr>
<tr>
<td>Stromal hemosiderin disposition</td>
<td>32%</td>
</tr>
<tr>
<td>Glandular metaplasia</td>
<td>9%</td>
</tr>
<tr>
<td>Stromal necrosis</td>
<td>7%</td>
</tr>
<tr>
<td>Reactive atypia in surface glands</td>
<td>4%</td>
</tr>
<tr>
<td>Stromal calcification</td>
<td>1%</td>
</tr>
</tbody>
</table>
The initial changes in the endometrium caused by Mirena® may be associated with irregular bleeding or spotting, particularly in the first few months of treatment. Although the mechanism underlying irregular bleeding or spotting with hormonal therapy is not well understood, it may involve matrix metalloproteinases and their tissue inhibitors, and/or a hormonal influence upon endometrial sex steroid receptors, or ligand availability in the endometrium. With Mirena®, once the endometrial effects are established, the bleeding becomes less in quantity than usual, or may cease altogether.

Mirena® may also induce the release of the binding protein for endometrial insulin-like growth factor I, thus inhibiting its growth-promoting effect. This may explain the protective effect of Mirena® on fibroid formation reported by Sivin & Stern. An alternative explanation may be that the thin estrogen-resistant endometrium will not produce enough growth factors to stimulate the growth of fibroids.

The morphological changes in the endometrium revert to ‘normal’, and menstruation has been reported as early as the first month following removal of Mirena®. After an initial increase in spotting during the first few months of use, Mirena® brings about a highly significant reduction in days of bleeding and/or spotting (Figure 3). In the study by Nilsson et al., a significantly greater proportion of women in the Mirena® group than in the copper intrauterine device (Cu-IUD; NOVA T) group reported an improvement in dysmenorrhea (35% vs 9%; p<0.005).

![Figure 3. Mean number of days of a) spotting and b) bleeding, during the initial 12 months' use of Mirena® and Nova T.]
In a study comparing the effects of Mirena® and the Cu-IUD (Nova T) 3 months after insertion, the volume of menstrual bleeding decreased by 60% in users of Mirena®, whereas it increased by 90% in users of the Cu-IUD. Mean menstrual blood loss following insertion of Mirena® also differed from that after insertion of the Cu-IUD (Multiload Cu250: reduction of >75% vs increase of >50%; p<0.001) in women with normal pre-insertion menstruation (Figure 4). 2

**Figure 4.** Change in measured menstrual blood loss (mL/menses) with Mirena® and a copper intrauterine device (Cu-IUD; Multiload Cu250) during 12 months of use. 2

The number of bleeding days in women with normal blood loss is reduced by Mirena®. 3 Approximately 20% of women using the system for contraception experience amenorrhea (defined as the absence of bleeding or spotting within the last 90 days) within 1 year. The blood hemoglobin levels and serum ferritin levels in ‘normal’ women also respond positively to the marked reduction in blood loss brought about by the system.

During the first year of a second consecutive period of Mirena® use, bleeding is further reduced, compared with the first 5-year period. 5,41,42 Many women become free of bleeding soon after the second Mirena® insertion, and the initial period of spotting that occurred after the first Mirena® insertion does not typically recur (Figure 5). 1,41 Insertion of the second consecutive Mirena® was judged to be easy and associated with no or only mild pain in the vast majority of cases. Therefore, removal of a previous Mirena® and insertion of a second one at the same visit is easy, uncomplicated and practical, and, thus, should be the standard of care. 43

**Figure 5.** Bleeding pattern with continuous long-term use of Mirena®. The bars show the bleeding patterns at the end of the first 5-year period and the second 5-year period. 5

### 3.1.3. Ovarian function

During the first year of use, some women experience suppression of ovarian function. Thereafter, most cycles are ovulatory, 23 and the incidence of ovulatory cycles with Mirena® and with the Cu-IUD (Multiload Cu250) is the same (85%). 2 The effect of LNG on ovarian function depends on plasma LNG levels and there are marked interindividual differences in the plasma levels achieved. 24,28 In general, the anovulatory cycles (5–15% of treatment cycles) correlate with higher levels of LNG. 7,44
The gradual reduction of endometrial thickness and conversion of the functional endometrium to a rest stage resistant to estrogen stimulation is visible in the gradual reduction in menstrual blood loss during the first few months. Oligomenorrhea develops, despite normal ovarian function. No difference in the incidence of ovulation is found between menstruating and amenorrheic women.²⁸

### 3.2. Menorrhagia

Regular excessive bleeding (menorrhagia), defined as menstrual blood loss >80 mL, is usually associated with ovulatory cycles. Erratic heavy bleeding may signify anovulatory cycles. LNG is a very potent blocker of estrogen activity on the endometrium.⁴⁶ Mirena® delivers LNG locally to the uterine cavity and over an initial 3–6 months' use it gradually reduces the thickness and vascularity of the endometrium. Although the resulting reduction in blood loss occurs in all women (regardless of their menstrual blood loss before using Mirena®), its therapeutic significance is most important in women with menorrhagia.

### 3.3. Protection from endometrial hyperplasia during ERT

The role of Mirena® in HRT is to prevent estrogen-induced endometrial hyperplasia, thereby protecting against the development of endometrial carcinoma. This is achieved by delivering a high concentration of LNG direct to the endometrium, which results in inactivity of the epithelial layer, glandular atrophy, and pseudodecidual or decidual transformation of the stromal layer.²⁹,⁴⁷⁻⁵² Mirena® delivers LNG locally to the uterine cavity and over an initial 3–6 months’ use it gradually reduces the thickness and vascularity of the endometrium. Although the resulting reduction in blood loss occurs in all women (regardless of their menstrual blood loss before using Mirena®), its therapeutic significance is most important in women with menorrhagia.

There is no reduction in E₂ levels during the use of Mirena®. Figure 6 shows the mean plasma E₂ and LNG concentrations in menstruating and amenorrheic women.²⁴ Menstrual bleeding does not itself reflect ovarian function among women using Mirena®: not only are average progesterone levels the same among those with regular, scanty bleeds as those with oligomenorrhea, but the levels of E₂ and the incidence of ovulation are similar for the two groups.²⁴

Figure 6. Mean plasma estradiol and levonorgestrel concentrations (pg/mL) in menstruating and amenorrheic women using Mirena® for 1 or 2 years.²⁴

The gradual reduction of endometrial thickness and conversion of the functional endometrium to a rest stage resistant to estrogen stimulation is visible in the gradual reduction in menstrual blood loss during the first few months. Oligomenorrhea develops, despite normal ovarian function. No difference in the incidence of ovulation is found between menstruating and amenorrheic women.²⁸
4. Pharmacokinetics

**KEY POINTS:**

- Mirena® releases levonorgestrel (LNG) directly into the uterus resulting in high concentrations of LNG in the endometrium

- Intrauterine administration of LNG with Mirena® results in lower systemic exposure than with conventional oral administration

- The continuous release of LNG from Mirena® avoids ‘peaks and troughs’ in serum levels
4. Pharmacokinetics

The pharmacokinetics of LNG have been extensively studied and reported in the literature. The bioavailability of orally administered LNG is about 90%. A half-life of 20 hours is considered the best estimate, although some studies have reported values as short as 9 hours and others as long as 80 hours. Another finding, although in agreement with experience with other synthetic steroids, has been of marked differences in metabolic clearance rate among individuals, even when administration was by the intravenous route. LNG is extensively metabolized to a large number of inactive metabolites.

Mirena® releases LNG into the uterine cavity, from where it is quickly absorbed via the capillary network in the basal layer of the endometrium into the systemic circulation. In women of reproductive age, LNG can be detected in the plasma after one hour. Maximum plasma LNG concentrations are reached within two weeks of insertion. Studies assessing the long-term use of Mirena® have shown that the LNG concentrations in plasma gradually decline over time (Figure 7).

The plasma LNG achieved with Mirena® is lower than that with Norplant®, the combined oral contraceptive and the mini-pill and, unlike with oral contraceptives, the levels with Mirena® do not display peaks and troughs (Figure 8). Although LNG concentrations are fairly stable, there is a marked inter-individual variation.

Figure 7. Serum levonorgestrel (LNG) concentrations in women of reproductive age weighing above 55 kg (median, 25% [Q1] and 75% [Q3] percentiles).

Figure 8. Schematic comparison of levonorgestrel (LNG) plasma concentrations for four different methods of contraception.
Plasma LNG is mainly bound to sex hormone-binding globulin (SHBG), a plasma-binding protein with an affinity for endogenous sex hormones (dihydrotestosterone, testosterone and E₂) and LNG. Bodyweight and serum SHBG concentration have been shown to affect systemic LNG concentration, i.e. low bodyweight and/or high SHBG levels increase LNG concentration. In women of reproductive age with a low bodyweight (37 to 55 kg) the median serum concentration of LNG is about 1.5-fold higher than in those weighing above 55 kg. Figure 9 shows the positive correlation between concentrations of plasma LNG and SHBG, and it is thought that SHBG may delay the metabolic degradation of LNG. Higher levels of SHBG (and LNG) are found in women with anovulatory cycles, suggesting that these women have a greater degree of ovarian suppression.

LNG is associated with a high affinity to SHBG, and SHBG levels are sensitive to changes in estrogen levels. Consequently, when LNG and estrogen are administered together, estrogen will affect levels of SHBG, which will directly influence the serum levels and biological activity of LNG. In post-menopausal women using Mirena® together with non-oral estrogen treatment, the median serum concentrations of LNG declines from 257 pg/mL (25th to 75th percentiles: 186 pg/mL to 326 pg/mL) at 12 months to 149 pg/mL (122 pg/mL to 180 pg/mL) at 60 months. When Mirena® is used together with oral estrogen treatment, the serum LNG concentration at 12 months is increased to approximately 478 pg/mL (25th to 75th percentiles: 341 pg/mL to 655 pg/mL), due to the induction of SHBG by oral estrogen treatment. However, the level of LNG in post-menopausal women is significantly lower with Mirena® than with sequential oral HRT containing LNG 250 µg/day (Figure 10). The high local drug exposure in the uterine cavity, which is important for the local action of Mirena® on the endometrium, leads to a strong concentration gradient via the endometrium to the myometrium (gradient endometrium to myometrium >100-fold), and to low concentrations of serum LNG (gradient endometrium to serum >>1000-fold). Oral administration of LNG in a dose 10 times that of the intrauterine system results in uniform concentrations of LNG throughout the endometrium and adjacent tissues, with the result being that the effects on the endometrium are weaker than those achieved by intrauterine delivery.
5. Indications

KEY POINTS:

- Mirena® provides highly reliable long-term reversible contraception for up to 5 years – its efficacy is comparable to female sterilization

- Mirena® is a highly effective treatment for menorrhagia, markedly reducing menstrual blood flow and replenishing body iron stores and hemoglobin levels

- Mirena® effectively prevents endometrial hyperplasia during estrogen replacement therapy (ERT)
5. INDICATIONS

5.1. Contraception

Mirena® is a highly reliable contraceptive. Its efficacy is comparable to female sterilization, although reversible, and it has the advantage of being easy and convenient to use. It has been said that Mirena® was developed to combine the benefits of oral and intrauterine contraceptives – reliability and simplicity. Indeed, Andersson et al. describe Mirena® as being one of the most reliable long-term reversible contraceptive methods requiring single application. Unlike oral contraceptives, which may be associated with poor compliance, the efficacy of Mirena® is not influenced by patient compliance.

5.2. Menorrhagia

In addition to its contraceptive effects, Mirena® also markedly reduces menstrual blood flow (by up to 97%) and alleviates dysmenorrhea. The reduction in menstrual blood flow is of particular value in women with menorrhagia. In this situation, Mirena® has proved to be effective in reducing menstrual losses, replenishing body iron stores and restoring hemoglobin levels. Menorrhagia is an approved indication for Mirena® in most countries where it is licensed for contraception.

5.3. Protection from endometrial hyperplasia during ERT

Studies in peri- and post-menopausal women have shown that Mirena® exerts a strong, localized progestogenic effect on the endometrium that effectively prevents endometrial hyperplasia (the first step in the development of endometrial cancer) during ERT. With Mirena® in situ, menopausal women have the freedom to choose the type, route of administration and dose of estrogen most appropriate to their needs, preferences or lifestyles. Protection from endometrial hyperplasia during ERT is also an approved indication for Mirena® in most countries where it is licensed for contraception.
6. Contraception

**KEY POINTS:**

- Mirena® has a low failure rate of approximately 0.2% at 1 year and a cumulative failure rate of approximately 0.7% at 5 years
- Mirena® is an effective contraceptive for breast-feeding women and does not affect infant development
- Mirena® is one of the most cost-effective long-term contraceptives available
- Mirena® is associated with high user satisfaction and continuation rates in routine clinical practice
- Mirena® is associated with shorter and lighter menstrual bleeding
- Appropriate counseling before insertion of Mirena® results in high continuation rates and user satisfaction
6.1. Efficacy in clinical trials

The contraceptive efficacy of Mirena® has been assessed both in comparative studies to copper intrauterine devices (Cu-IUDs) and oral contraceptives, and in non-comparative studies. The failure rate of Mirena® is approximately 0.2% at 1 year and the cumulative failure rate is approximately 0.7% at 5 years. In large, comparative multicenter trials the first-year gross pregnancy rate has been 0–0.2%, and the cumulative rate over 5 years has been 0.5–1.1% (Table 2).

Table 2. Summary of non-comparative and comparative efficacy studies with Mirena® at 1 and 5 years’ duration.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Contraceptive method</th>
<th>No. of women (n)</th>
<th>Duration of study (years)</th>
<th>Cumulative gross ratea per 100 women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pregnancy</td>
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<td>NON-COMPARATIVE STUDIES</td>
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<td>Scholten2</td>
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<tr>
<td>Thiery et al.9</td>
<td>Mirena®</td>
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<td>1</td>
<td>1.0</td>
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<tr>
<td>Dubuisson et al.10</td>
<td>Mirena®</td>
<td>203</td>
<td>1</td>
<td>0.0</td>
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<tr>
<td>COMPARATIVE STUDIES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivin et al.11</td>
<td>Mirena® vs Cu T380 Ag</td>
<td>755 vs 754</td>
<td>1</td>
<td>0.3 vs 0.3</td>
</tr>
<tr>
<td>Sivin et al.11</td>
<td>Mirena® vs Cu T380 Ag</td>
<td>1124 vs 1121</td>
<td>5</td>
<td>1.1 vs 1.4</td>
</tr>
<tr>
<td>ICMR10</td>
<td>Mirena® vs Cu T380 Ag vs Cu T200C vs Cu T200C</td>
<td>475 vs 424 vs 500 vs 496</td>
<td>1</td>
<td>0.0 vs 0.8 vs 0.9 vs 0.0</td>
</tr>
<tr>
<td>Nilsson et al.11</td>
<td>Mirena® vs Nova T</td>
<td>164 vs 156</td>
<td>1</td>
<td>0.6 vs 2.6</td>
</tr>
<tr>
<td>Luukkainen et al.12</td>
<td>Mirena® vs Nova T</td>
<td>164 vs 156</td>
<td>5</td>
<td>0.8 vs 6.7</td>
</tr>
<tr>
<td>Luukkainen et al.12</td>
<td>Mirena® vs Nova T</td>
<td>1821 vs 937</td>
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<tr>
<td>Andersson et al.13</td>
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<td>1821 vs 937</td>
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<td>Gao et al.14</td>
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<tr>
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<td>Mirena® vs COCs</td>
<td>94 vs 99</td>
<td>1</td>
<td>0.0 vs 0.0</td>
</tr>
</tbody>
</table>

Gross rates are estimates of the cumulative probability of an event, such as pregnancy or expulsion, computed by life table or actuarial methods. Gross rates are unaffected by the rates at which competing events occur; net rates allow the presence of competing risks of termination of use, e.g. for bleeding/pain. Definitions from Tietze et al.84

In an earlier 5-year comparative study of Mirena® and the Cu-IUD,35 the results were comparable with the large study: the 5-year pregnancy rate was 0.8% for Mirena® and 6.7% for the Cu-IUD (see Table 2).

The Cu T380 is considered one of the most reliable Cu-IUDs. Sivin and colleagues compared the contraceptive reliability of Mirena® and the Cu T380 Ag (a model with silver-cored wire) for up to 7 years76,77,85,86 in a large, multicenter study. The two methods had similar contraceptive reliability, the pregnancy rates for each being 0.3% at 1 year, increasing to 1.1% (Mirena®) and 1.4% (Cu-IUD) at 5 years (see Table 2). One of the two pregnancies reported during the first year with Mirena® occurred after an unnoticed expulsion. Expulsion rates declined year-on-year for both Mirena® and the Cu-IUD, the first year accounting for the majority of all expulsions. The expulsion rate also declined with increasing age at insertion of the devices.
The World Health Organization assessed the clinical efficacy of Mirena® compared with Cu T380 Ag in a multicenter study involving 3815 insertions. The pregnancy rate after 6 years of use (interim data to 30 September 2003) was 0.5 (standard error 0.2) per 100 women with Mirena®, compared with 2.0 (standard error 0.5) in the Cu-IUD group.87

The pregnancy rate for Mirena® in everyday use has been assessed in a post-marketing study involving over 17,000 women during 58,600 woman-years of use. The medical records of a total of 108 unplanned pregnancies were reviewed, and in 64 pregnancies conception occurred with Mirena® in situ.62 The 5-year cumulative pregnancy rate was 0.5 per 100 users and the 5-year Pearl rate was 0.11.62

The pregnancy rate in the first 12 months is expected to be approximately 0.1–0.3 for oral contraceptives during perfect use.88 However, the failure rate can be up to 8% in typical use due to non-compliance.89 By contrast, Mirena® does not rely on patient compliance for its contraceptive reliability, and, expulsions apart, its expected and actual pregnancy rates should therefore be identical.

A large retrospective multicenter case-control study that compared the efficacy of various intrauterine contraceptives (IUCs) showed that Mirena® was the most effective IUC.90 The age-adjusted odds of pregnancy, with Mirena® as the reference group with an odds ratio of 1.0, were increased by a multiple of 2.70 (95% confidence interval [CI] 1.11–6.56) for IUDs with a copper surface area of 375–380 mm² (Gyne T380, MLCu375 and Gynelle 375), 8.45 (95% CI 3.19–22.39) for IUDs with a copper surface area of 300 mm² (Sertalia), 7.20 (95% CI 3.01–17.22) for IUDs with a copper surface area of 200 mm² and a silver core (Nova T), and 24.43 (95% CI 4.73–126.20) for the GyneFix® device.

6.1.1. Post-partum use

After childbirth, the question of contraception arises again. It is not advisable for breast-feeding women to use combined oral hormonal contraception because the contraceptive hormones that do cross into breast milk may affect the infant and may also reduce the volume of milk produced.91 In general, progestogen-only methods do not appear to affect the quality or quantity of breast milk; therefore, they are approved for use during lactation. In Mirena® users, only approximately 0.1% of the levonorgestrel dose is transferred to the infant during breast-feeding.92 A recent randomized study compared the performance of Mirena® (n=163) and a Cu-IUD (Cu T380 Ag) (n=157) in lactating women.92 The insertions were performed 6–8 weeks after delivery. The continuation rates with both devices were equal, and no between-group differences were found in the rates of breast-feeding continuation, complete weaning, full breast-feeding and partial breast-feeding (Figure 12). Furthermore, the infant physical growth parameters and various infant developmental tests were similar.92

Figure 12. Breast-feeding performance following insertion of Mirena® or the Cu T380 Ag IUD.92

These studies support the use of Mirena® in the post-partum period, with no negative effects on breast-feeding performance and infant development. Because the uterine wall may be softer in the post-partum period, IUD or IUS insertions during this period should be performed with particular caution to avoid perforation.

6.1.2. Use of Mirena® in nulliparous women

Mirena® is generally not considered the method of first choice for nulligravid women. However, it may be a suitable option for those carefully selected young nulliparous women not at risk of sexually transmitted infections. Suhonen et al.93 compared the clinical performance of Mirena® (n=94) with combined oral contraceptives (n=99) in young nulliparous women aged 18–25 years. Both methods were well tolerated and no pregnancies occurred in either group over the 12 months of follow-up. Bleeding and spotting were more common with Mirena® use during the first 3 months, but decreased significantly during continued treatment. During the last 3 months, 21% of women using Mirena® were amenorrheic compared with 1 woman in the combined oral contraceptive group. Moreover, 90% of women in the Mirena® group rated Mirena® as moderate to very good, compared with 88% in the combined oral contraceptive group. Of the women who completed the study, 88% of Mirena® users and 68% of the oral contraceptive users were willing to continue with the same method.
In a retrospective general practice study assessing the performance of mainly Cu-IUDs (and a small cohort of Mirena® users) in the Netherlands, there was no difference between nulliparous and parous women with regard to IUD complications, such as pelvic inflammatory disease (PID) or expulsion.

Recently, the Society of Family Planning concluded in their clinical guideline that nulliparous women desiring effective contraception should be considered candidates for IUDs. This review assessed common concerns related to the use of Mirena® and the Cu T380 Ag IUD in nulliparous women. The guideline concluded that:

- Mirena® and the Cu T380 Ag (ParagardTM) are effective and safe contraceptive devices for nulliparous women.
- Mirena® and ParagardTM have comparable or higher continuation rates of use in nulliparous women when compared to other methods of contraception.
- Mirena® and ParagardTM do not increase the risk of pelvic infection or infertility, and Mirena®, in particular, reduces the risk of pelvic infection.
- Due to expulsion rates and bleeding profile, Mirena® may be better tolerated than ParagardTM in nulliparous women.

6.1.3. Post-abortal use

Women who seek an abortion are highly motivated to prevent a further unplanned pregnancy. However, only approximately one-half of women who underwent abortion attended the post-abortion follow-up visit in one study. Therefore, a method that can be initiated at the time of abortion and does not depend on user motivation for its reliability – such as Mirena® – is preferable.

Several studies suggest that Mirena® is an effective post-abortion contraceptive. Pakarinen et al.1 showed that long-term Mirena® use (n=305) following first trimester abortion (termination at ≤ 12 weeks’ gestation) provided more effective contraceptive protection than a Cu-IUD (Nova T, n=133) in a randomized study. The cumulative pregnancy rate per 100 women at 5 years was 0.8 for Mirena® compared with 9.5 for the Cu-IUD. Although both devices were well tolerated when inserted immediately after abortion, the incidences of device expulsion, bleeding, pain and PID tended to be lower with Mirena®. However, the expulsion rate of both devices was higher than after interval (post-menstrual) insertion, with a 5-year cumulative expulsion gross rate of 15.4% for the Cu-IUD and 10.5% for Mirena®. A prospective observational study assessing immediate IUC after first-trimester medical abortion reported IUD expulsion in 4.1% (4/97) of women during 3 months’ follow up. In addition, there were no pelvic infections, pregnancies, or uterine perforations. The insertion of Mirena® can also be performed at the post-abortion follow-up visit at approximately 3 weeks after a medical abortion.

There is convincing evidence showing that immediate post-abortion IUC is more effective than non-IUC or short-acting hormonal contraception in reducing the occurrence of repeat unintended pregnancy and abortion.

6.1.4. Long-term consecutive Mirena® use

Long-term clinical experience following consecutive use of Mirena® was assessed in a 15-month multicenter prospective study after approximately 5 years of use.41,42 The removal and replacement of Mirena® was rated as easy in 97% (111/115) and 87% (100/115) of investigators, respectively (Figure 13). Pain on removal was rated as none-to-mild, moderate, or severe by 88.7%, 9.6% and 1.7% of women, respectively. During insertion, no or mild pain was reported by 61.7% of women, moderate pain reported by 31.3% and severe pain reported by 7.0% of women (Figure 14). Apart from the limited bleeding/spotting associated with the insertion procedure of the second Mirena®, further reductions in the number of bleeding and spotting days were generally observed during the second consecutive use of Mirena®. However, women with uterine fibroids or any bleeding at baseline continued to experience more bleeding/spotting than other women. In contrast, factors such as age, parity, body mass index, indication of Mirena® use (contraception or heavy menstrual bleeding) or smoking were not identified as predictors for bleeding/spotting patterns with consecutive Mirena® use. There were no pregnancies and only one case of expulsion was reported. Only 5.9% (12/115) of women prematurely discontinued the study.

Figure 13. Physicians’ assessment of ease of insertion of the second Mirena®.
A double-blind, placebo-controlled subset of the 15-month prospective multicenter study investigated the effect of misoprostol on the ease of consecutive Mirena® insertions. In this subset, women received a sublingual dose of 400 mcg misoprostol or placebo 3 hours prior to their second Mirena® insertion. The proportion of insertions rated as easy by the investigators for the misoprostol group (93% [40/43]) was not significantly different than for the placebo group (91% [42/46]; p=1.0). Although, cervical priming with misoprostol may be beneficial for some women before Mirena® insertion, routine use of misoprostol to facilitate Mirena® insertion in women with a previous successful insertion is unnecessary, and increases adverse events related to the study drug on the day of insertion.

6.1.5. Cost-effectiveness in contraception

All long-acting reversible contraceptives, including Mirena®, are cost-effective compared with combined oral contraceptives or the male condom. As with any contraceptive method, the continuing cost-effectiveness of Mirena® is sensitive to large changes in the cost of the system relative to the costs associated with unintended pregnancies.

6.2. Tolerability in clinical trials

Just as the efficacy of a contraceptive method is evaluated in terms of the rates of accidental pregnancy and expulsion, it is customary to describe the tolerability of intrauterine contraceptive methods in terms of continuation rates and rates of removal for adverse events and complications, such as bleeding, pain, perforation, ectopic pregnancy and infection. Most of the studies described previously that assessed the efficacy of Mirena® also presented tolerability data for the system. In addition, several studies have specifically addressed the safety issues of using Mirena® (Table 3).

Table 3. Comparison of discontinuation rates with Mirena® and copper intrauterine devices (Cu-IUDs) in two separate 5-year studies. Study A: 5-year gross cumulative discontinuation rates per 100 women with Nova T (n=937) and Mirena® (n=1821); Study B: 1- and 5-year gross annual discontinuation rates per 100 women for Cu T380 Ag (n=1121) and Mirena® (n=1124).

<table>
<thead>
<tr>
<th>Event</th>
<th>Study</th>
<th>1 year</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cu-IUD</td>
<td>Mirena®</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>A</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Expulsion</td>
<td>A</td>
<td>3.9</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>5.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>A</td>
<td>0.0</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Bleeding problems</td>
<td>A</td>
<td>6.3</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>6.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Other menstrual/pain</td>
<td>A</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Hormonal</td>
<td>A</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PID</td>
<td>A</td>
<td>3.1</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>3.9</td>
<td>4.5</td>
</tr>
<tr>
<td>Other medical</td>
<td>A</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Planning pregnancy</td>
<td>A</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Other personal</td>
<td>A</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>81.8</td>
<td>76.3</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01; *** p<0.001. NR = not reported; PID = pelvic inflammatory disease.
Two 5-year studies revealed a higher continuation rate with Mirena® (53 per 100 and 47 per 100; Luukkainen et al.80 and Andersson et al.,40 respectively), compared with a Cu-IUD (Nova T, 50 per 100 and 45 per 100). Andersson et al.40 showed that the continuation rate was higher in the older age group for both contraceptive methods. In contrast, when compared with another Cu-IUD (Cu T380 Ag) over 5 years of use, Mirena® had a lower continuation rate (33.0 per 100 vs 40.6 per 100), the main contributor to the difference being terminations related to amenorrhea in the Mirena® group.77

Nevertheless, a 5-year continuation rate of 53 per 10080 is high, especially in view of the fact that during the first, double-blind study patients did not receive method-related counseling regarding the bleeding pattern they could expect. The impact of such counseling is demonstrated by a later post-marketing study involving over 17,000 Mirena® users, in which continuation rates were 93% at 1 year and 65% at 5 years.23 A multivariate analysis showed that excessive bleeding and spotting carried the highest relative risk ratio for discontinuation (2.77), whereas occasional or total absence of menstruation carried the lowest (0.46).23 The authors point out that once women have been reassured that infrequent or absent bleeding is benign, they regard it as an advantage. Hence, amenorrhea-related discontinuation rates are lower in studies that incorporate counseling.

An analysis by Pakarinen et al.1 shows that the performance of Mirena® is acceptable in women who have the system fitted after an induced abortion. The rates of discontinuation for bleeding and/or pain were similar to those with Cu-IUDs.

Continuation rates are also high in those women who have not been satisfied with their previous contraceptive method and who switched to Mirena®. In a group of 35- to 45-year-old women who switched to Mirena® because they were dissatisfied with their previous contraceptive (mainly Cu-IUDs or oral contraceptives) or had poor tolerance, the continuation rate with Mirena® after 12 months’ treatment was about 90%.77 The continuation rates with Mirena® were similar in women who switched from Cu-IUDs and in women who switched from oral contraceptives (Figure 15). Similarly, Shain et al.103 demonstrated that more than 70% of recipients reported greater satisfaction with Mirena® than with their previous contraceptive methods.

User satisfaction with Mirena® is high in routine clinical practice: a survey of over 17,000 Mirena® users revealed that 74% of women were satisfied with Mirena®, with user satisfaction increasing with age.104

6.2.1. Adverse effects

During the first few months after insertion of Mirena®, the recipient may experience transient hormonal adverse effects including edema, headache, breast tenderness and acne or other skin problems.24 These adverse effects have been categorized by medical dictionary for regulatory activities (MedDRA) system organ classes (Table 4).12 Functional ovarian cysts may occur, as with other progestogen-only methods of contraception.105 The rate of discontinuation with Mirena® because of bleeding problems is similar to or lower than that with Cu-IUDs in randomized clinical trials (see Table 3). In contrast, discontinuations due to amenorrhea and hormonal adverse effects are more frequent with Mirena® (see Table 3). The bleeding pattern during Mirena® use is discussed in detail in section 6.2.3.
6.2.2. Safety

Luukkainen\(^\text{45}\) reported that, in long-term studies comparing the effects of Mirena\(^\text{®}\) and Cu-IUDs, the use of Mirena\(^\text{®}\) results in significantly higher levels of hemoglobin, serum ferritin and serum protein than the use of Cu-IUDs, whereas there is no significant effect on serum lipids, carbohydrates, liver enzymes or the coagulation system. In these 5-year studies, no effect on blood pressure or bodyweight was demonstrated.\(^\text{14}\) This good safety record has been maintained during long-term use.\(^\text{5}\)

Some studies with Mirena\(^\text{®}\) have shown a low PID incidence (see Table 3). According to current knowledge, the risk of PID associated with IUD/intrauterine system (IUS) use is considered to be slightly elevated only during the first post-insertion month, whereafter the risk decreases to the background level.\(^\text{106}\) In a large randomized study, the gross cumulative PID rate was 0.8% at 5 years, which was significantly lower than that with a Cu-IUD (2.2%, \(p \leq 0.01\)).\(^\text{40}\) Therefore, some authors suggest that the system offers protection against PID, which could be related to the thickening of cervical mucus (preventing ascending infection), endometrial suppression or reduced bleeding.\(^\text{60}\) However, a lower PID rate with Mirena\(^\text{®}\), as compared to Cu-IUDs, has not been observed in all randomized studies with Mirena\(^\text{®}\).\(^\text{76,77,85}\)

The ectopic pregnancy rate of Mirena\(^\text{®}\) is among the lowest of the intrauterine contraceptive methods.\(^\text{12}\) This rate is also lower than the rate for a control population of sexually active women not using contraception (0.3–0.5% per year).\(^\text{13}\) Although the absolute risk of ectopic pregnancy in Mirena\(^\text{®}\) users is low, an ectopic pregnancy must be ruled out in the case of an accidental pregnancy during Mirena\(^\text{®}\) use.\(^\text{21}\)

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Careful attention has been paid to the cervical cytology of users of Mirena\(^\text{®}\). Annual cervical smears over a period of 6 years have revealed no difference in cytology between users of Mirena\(^\text{®}\) and users of a Cu-IUD,\(^\text{14}\) and extensive studies show that the incidence of cervical dysplasia is not increased in women using Mirena\(^\text{®}\) or a Cu-IUD.\(^\text{107}\)

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**Table 4. Adverse effects of Mirena® categorized by medical dictionary for regulatory activities (MedDRA) system organ classes.\(^\text{12}\)**

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
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<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Gastrointestinal disorders</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td></td>
<td></td>
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<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
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<td></td>
<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Investigations</td>
<td></td>
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</tbody>
</table>

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

* Endometrial protection trials: “common”; ** Endometrial protection trials: “very common”

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Low risk of pelvic inflammatory disease

Ectopic pregnancy rate with Mirena® is lower than in sexually active women not using contraception
Mirena® is not associated with adverse effects on lipid metabolism. In addition, although Mirena® was shown to increase the occurrence of impaired fasting glucose, the impairment did not increase to dangerous levels and impaired glucose tolerance was not reported. Moreover, control of diabetes does not appear to be adversely affected by Mirena®. Rogovskaya et al. reported no important differences in glycosylated hemoglobin levels, fasting serum-glucose levels, or daily insulin requirements between Mirena® and Cu-IUD users over 12 months’ treatment in women with type 1 diabetes.

Since breast cancer is a hormone-dependent tumor, women who have breast cancer should use non-hormonal methods of contraception, and breast cancer is a contraindication for Mirena® use. However, available data suggest that Mirena® use is not associated with an increased risk of the development of breast cancer. Although the incidence of breast cancer increased with age during a large post-marketing study assessing over 17,000 users, the rate was no different from that of the average female population. A population-based, case-control study of 5133 breast cancer cases in Finnish and German registries showed that current or ever use of Mirena® was not associated with an increased risk of breast cancer compared with Cu-IUD users (Table 5). In addition, there was no evidence of tumor promotion or induction with Mirena® use.

<table>
<thead>
<tr>
<th>Table 5. Breast cancer odds ratios (ORs) for ever use and current use of Mirena® vs copper intrauterine devices.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ever use</strong></td>
</tr>
<tr>
<td>OR Crude</td>
</tr>
<tr>
<td>Adjusted expert model*</td>
</tr>
<tr>
<td><strong>Current use</strong></td>
</tr>
<tr>
<td>0.90</td>
</tr>
</tbody>
</table>
| Adjusted for body mass index, family history of breast cancer, age at first birth, age at menarche, and physical activity.

Difficulties with the insertion of Mirena® may occur in some women, especially nulliparous and post-menopausal women. In a clinical study of nulliparous women, Suhasen et al. reported a difficult insertion in 15% of cases and 13% required paracervical blockade and/or dilatation. Pain at insertion was reported as severe in 21% of nulliparous women and in 3.6% in parous women. Harrison-Woolrych et al. reported a higher rate of insertion difficulties with Mirena® compared with a Cu-IUD (Multiload Cu 375); however, the rate of insertion difficulties for both devices (3.6% and 1.3%, respectively) was low.

A potentially serious complication associated with the insertion of Mirena® is uterine perforation, the incidence of which is less than 1 per 1000 insertions. The risk of perforations may be increased in post-partum insertions, in lactating women, and in women with fixed retroverted uterus. Post-partum insertions should be postponed until the uterus is fully involuted, however not earlier than 6 weeks after delivery. If involution is substantially delayed, waiting until 12 weeks post-partum should be considered. In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation. The incidence of uterine perforation with Mirena® appears to be similar to that observed with Cu-IUDs.

6.2.3. Changes in bleeding pattern

Hormonal contraceptives often produce changes in the established menstrual bleeding pattern, which influences a woman’s decision to choose or continue with a particular method. A telephone survey among 1300 women in the Netherlands found that 80% would prefer a change to lighter, shorter or less painful menstruation. Thus, the bleeding pattern induced by Mirena® will have an impact on its acceptability and continuation. Excessive bleeding and spotting are associated with premature removal of Mirena®, but those who have occasional or total absence of periods are unlikely to discontinue.

A fairly predictable bleeding pattern follows the insertion of Mirena® (see Figure 3). The first few months are characterized by an increase in total bleeding days (menstrual days and inter-menstrual spotting days combined), an effect that is also seen in users of Cu-IUDs. After the first 3 months, however, the menstrual blood loss decreases and the number of bleeding days declines.
Thorough counseling and discussion before the insertion of Mirena® will result in high continuation rates and user satisfaction. Information received at the insertion visit, particularly with regard to the possibility of occasional missing periods, has been shown to improve the level of user satisfaction. Women should be informed that Mirena® will produce changes in menstruation patterns during its use, including:

- irregular spotting and scanty bleeding, with a gradually decreasing total bleeding volume during the first 3–6 months.
- no monthly bleeding at all within the first year of use (in some 20% of women).

Counseling can be aided by the use of simple and easy-to-understand diary cards to keep track of the changes in bleeding pattern. Adequate counseling helps women to understand and accept the change in their bleeding pattern as a positive health benefit: the advantages of diminished monthly bleeding, duration of bleeding and dysmenorrhea are supported by the positive and objective benefits of increased hemoglobin and ferritin levels. Women using Mirena® should be reassured that the absence of bleeding is most unlikely to signify pregnancy (in case of doubt a pregnancy test should be performed). Similarly, women should be advised that the absence of bleeding is not indicative of a hormonal abnormality. They can also be assured that normal menstrual bleeding will return within the first month of Mirena® being removed.

6.2.4. Return to fertility

The preservation of reproductive capacity is critical to the acceptability of a contraceptive method. This is particularly the case for long-term methods such as Mirena®.

An early study asserted that cyclic ovarian function is ‘immediately restored’ after removal of Mirena®. Several more recent studies confirm that fertility rapidly returns to normal after the removal of Mirena®, with the 12-month cumulative conception rate being as high as 96 per 100 (range 79–96/100). The pregnancy rates after Mirena® removal are similar to those observed after Cu-IUD removal (Figure 16).
7. Menorrhagia

KEY POINTS:

- Mirena® reduces menstrual blood loss by over 80% in women with confirmed menorrhagia
- Mirena® improves hemoglobin levels and body iron stores in women with menorrhagia
- Mirena® is an effective alternative to hysterectomy in the treatment of menorrhagia and is associated with significantly fewer costs
7. MENORRHAGIA

7.1. Efficacy in the treatment of idiopathic menorrhagia

Subjective assessment of menstrual blood loss can be misleading (since women who report excessive loss may in fact have a normal blood loss), but objective assessment presents practical problems. None the less, the diagnosis must be made and the cause determined. Neoplasia should be excluded in all cases, perhaps with the exception of the pubescent girl, as should uterine fibroids and polyps, pregnancy complications and medication (e.g. exogenous hormonal therapy). Anemia is a potential problem in these women, being the most common cause of anemia in the UK. To date, the management of menorrhagia has relied on pharmacological or surgical therapy. Current pharmaceutical options include non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. mefenamic acid), antifibrinolytics (e.g. tranexamic acid), danazol, progestogens and combined oral contraceptives. The surgical alternatives include hysterectomy and endometrial ablation or resection. Mirena® is the standard of care for the treatment of menorrhagia in women who prefer a convenient, non-daily treatment option, and is recommended as the first-line medical therapy by the UK National Institute for Health and Clinical Excellence (NICE).

7.1.1. Reduction of menstrual blood loss

Studies objectively evaluating the reduction in menstrual blood loss achieved with Mirena® treatment in women with menorrhagia suggest it reduces blood loss by ≥80% after 3 months of treatment, and that the reduction in menstrual blood loss is maintained up to 3 years of treatment (Table 6). Andersson and Rybo64 demonstrated an 86% reduction in menstrual blood loss at 3 months after insertion and a 97% reduction at 1 year after insertion (Figure 17). Furthermore, mean hemoglobin concentrations had increased significantly after 6 months and 1 year of use, with mean ferritin concentrations also increasing significantly after 1 year of use (Figure 18).

Table 6. Summary of comparative and non-comparative studies evaluating the effectiveness of Mirena® in the treatment of menorrhagia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (months)</th>
<th>Mean menstrual blood loss (mL)</th>
<th>Reduction in menstrual blood loss (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scholten²</td>
<td>7–12</td>
<td>119</td>
<td>17</td>
<td>–86</td>
</tr>
<tr>
<td>Andersson &amp; Rybo⁶⁴</td>
<td>3</td>
<td>176①</td>
<td>24①</td>
<td>–86</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>176①</td>
<td>15①</td>
<td>–81</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>176①</td>
<td>5①</td>
<td>–97</td>
</tr>
<tr>
<td>Milsom et al.⁶⁵</td>
<td>3</td>
<td>203</td>
<td>34</td>
<td>–82</td>
</tr>
<tr>
<td></td>
<td>6</td>
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<td>25</td>
<td>–88</td>
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<tr>
<td></td>
<td>12</td>
<td></td>
<td>9</td>
<td>–96</td>
</tr>
<tr>
<td>Tang &amp; Lo⁶⁶</td>
<td>1</td>
<td>183①</td>
<td>84①</td>
<td>–54</td>
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a. Median values. * p<0.05; ** p<0.01; *** p<0.005; **** p<0.001. NR = not reported. † Fibroid-related menorrhagia.
7. MENORRHAGIA

Milsom et al.65 studied the effects of Mirena®, tranexamic acid and flurbiprofen on menorrhagia. Mirena® proved significantly superior to both forms of oral treatment in reducing blood loss, and was the only treatment to reduce menstrual blood loss to <80 mL. In addition, the duration of bleeding was not altered by either tranexamic acid or flurbiprofen, and the frequency of side-effects with these forms of treatment was greater than with Mirena®.

Irvine et al.125 showed that Mirena® reduced menstrual blood loss by 94% after a treatment period of 3 menstrual cycles (Table 6), compared with 87% with oral norethisterone (5 mg three times daily from day 5 to 26 of the menstrual cycle). After this period of treatment 76% of women in the Mirena® group wished to continue with treatment, compared with only 22% in the oral norethisterone group, indicating better tolerability of Mirena®.

Reid and Virtanen-Kari126 showed that the median reduction in blood loss after 6 cycles in women using Mirena® was significantly greater than in women treated with mefenamic acid (96% and 17%, respectively).

More recently, in a randomized, controlled study by Kaunitz et al., Mirena® was shown to reduce menstrual blood loss more effectively than oral medroxyprogesterone acetate over 6 cycles of treatment in women aged 18 years or older with menorrhagia.128 The absolute change in median menstrual blood loss from baseline to study end was –129 mL and –18 mL with Mirena® and oral medroxyprogesterone acetate, respectively (Table 6). Furthermore, the proportion of women with successful treatment (defined as menstrual blood loss less than 80 mL and a 50% or greater reduction in menstrual blood loss from baseline) was significantly higher with Mirena® compared with oral medroxyprogesterone acetate; 85% versus 22%, respectively (p < 0.001).

Figure 17. Reduction in menstrual blood loss (MBL) in women with menorrhagia after 3, 6 and 12 months of Mirena® use

Figure 18. Mean a) hemoglobin and b) ferritin concentrations in women with menorrhagia after 3, 6 and 12 months of Mirena® use (ferritin concentrations were not assessed at 3 months)
7.1.3. Mirena® compared with surgical treatment

Mirena® represents a well tolerated, effective and less invasive alternative to endometrial ablation,14–18 endometrial resection19,20 or hysterectomy.21,22,64,67 Furthermore, it allows women to preserve their fertility and may therefore become the first-line treatment in women with menorrhagia.19,130 Anecdotal evidence suggests that Mirena® may be associated with a reduction in the number of hysterectomies performed in England.131

Mirena® has similar efficacy to endometrial ablation in the treatment of menorrhagia.18 In a randomized, comparative study, the reduction in the pictorial blood loss assessment chart (PBAC) score achieved with Mirena® was greater than that with endometrial ablation after 1 year of treatment (Figure 19). The rate of women requiring an alternative treatment method was similar in the two groups.18 A systematic review and meta-analysis of six randomized clinical trials conducted by Kaunitz et al. showed that Mirena® had similar therapeutic effects (as determined using PBAC scores) to endometrial ablation up to 2 years of follow-up.132 In addition, both Mirena® and endometrial ablation were generally associated with similar improvements in quality of life. In contrast to Mirena®, however, endometrial ablation was associated with a higher risk of perioperative and long-term complications.132

**Figure 19.** Reduction in menstrual blood loss (assessed by pictorial blood loss assessment chart [PBAC] score) with thermal balloon ablation and Mirena®

In a 5-year randomized comparison of Mirena® (n=119) and hysterectomy (n=117), quality-of-life scores, general and psychological health parameters (Figure 20), and hemoglobin and ferritin levels improved to a similar extent in both treatment groups.22 Women assigned to the two treatments were equally satisfied with their treatment at 5 years after randomization, with satisfaction rates of over 90% in each group.22

**Figure 20.** Change in general and psychological parameters in women randomized to Mirena® or hysterectomy for 5 years. Data obtained using the RAND-36 quality-of-life instrument (higher scores indicate better health-related quality of life).22
7.2. Tolerability in the treatment of idiopathic menorrhagia

Studies evaluating Mirena® for the treatment of menorrhagia have reported high patient satisfaction and continuation rates,22 which is similar to findings from studies of Mirena® in contraception.

In the same way as occurs during the use of Mirena® for contraception, intermenstrual bleeding and spotting are relatively common during the initial months of Mirena® use.67,125 In a randomized controlled trial assessing the use of Mirena® versus hysterectomy in the treatment of menorrhagia,67 30% of women reported amenorrhea or oligomenorrhea at 6 months and 42% reported intermenstrual bleeding. The incidence of amenorrhea or oligomenorrhea increased to 53% at 12 months, and intermenstrual bleeding decreased to 32%. At 5 years’ follow-up, about three-quarters of women experienced amenorrhea or oligomenorrhea, 19% of women reported irregular bleeding and 6% reported scanty regular bleeding.22 Around one-half of the women in the Mirena® group discontinued treatment during 5 years’ follow-up. These 5-year continuation rates are similar to those observed in women using Mirena® as a contraceptive device.80

The rate of patient satisfaction and the incidence of adverse events with Mirena® in women with menorrhagia are similar to those observed in women using Mirena® as a contraceptive device. Indeed, in the randomized study by Irvine et al.,125 patient satisfaction with Mirena® was significantly higher in the Mirena® group than in the norethisterone comparator group.

The incidence of adverse events with Mirena® in women with menorrhagia are similar to those observed in women using Mirena® as a contraceptive device. Indeed, in the randomized study by Irvine et al.,125 patient satisfaction with Mirena® was significantly higher in the Mirena® group than in the norethisterone comparator group.

Studies in women with menorrhagia suggest lipid variables remain unchanged when using Mirena®.108,134 Furthermore, clotting variables have been reported to remain unchanged at 3, 6 and 12 months after insertion.131 One study reported a significant reduction in mean diastolic blood pressure at 1 year after insertion, while no significant changes in systolic blood pressure were reported.108 Mean fasting plasma glucose levels were significantly increased in these patients at 1 year after insertion, but the levels attained were not deemed to be dangerous.
8. Protection from endometrial hyperplasia during ERT

KEY POINTS:

• Mirena® effectively protects the endometrium from hyperplasia during estrogen replacement therapy (ERT), regardless of estrogen formulation

• Mirena® is well tolerated by ERT users, as judged by high continuation rates

• Mirena® does not appear to counteract the favorable effects of ERT on the plasma lipid and lipoprotein profiles
8. PROTECTION FROM ENDOMETRIAL HYPERPLASIA DURING ERT

Hormone replacement therapy (HRT) is an acceptable option for providing estrogen to women who require relief of the symptoms caused by declining estrogen levels associated with the menopause (e.g. hot flushes, sweating, mood disturbances and vaginal dryness). For women with an intact uterus, additional progestogen is an obligatory requirement in order to protect the endometrium from estrogen-induced hyperplasia and cancer. Moreover, as the endometrium is the only tissue where the effects of progestogen are required, targeted delivery with Mirena® offers a logical and practical approach.

The efficacy of Mirena® in preventing estrogen-induced endometrial hyperplasia in peri- and postmenopausal women has been investigated in both comparative studies (vs established sequential and continuous combined regimens) and non-comparative studies.26,47,48,50–52,71–73,135 No endometrial hyperplasia has been detected in these trials, regardless of the dose or method of administration of the estrogen component, or the duration of therapy.26,47,48,50–52,71–73,135

Non-comparative follow-up studies in post-menopausal women indicate that the protective effects of Mirena® (as part of HRT) on the endometrium are maintained long term.26,52,71,73 In addition, Hampton et al.136 observed a non-proliferative endometrium in ≥95% of 82 peri-menopausal women and no endometrial hyperplasia throughout 5 years’ treatment with Mirena® in conjunction with continuous conjugated oral equine estrogen therapy. Moreover, the continuation rate at 5 years was 80% suggesting that the treatment regimen was well tolerated.

Although some bleeding and spotting commonly occur over the first 3 or 4 months of use, their incidence declines significantly over time. Indeed, at least half of users become amenorrheic by 6 months, increasing to over three-quarters at 1 year.71,135,137 This amenorrhea rate is then maintained to 5 years.25,26,52,135

Boon et al.138 reported continuation rates in peri-menopausal women using continuous oral estradiol (E2) plus Mirena® or an E2/norethisterone sequential regimen (Trisequens®). Continuation rates were higher with the Mirena®-based regimen from cycle 6 onwards, with the difference being statistically significant in favor of Mirena® by cycle 26 (82 vs 68%, p=0.028). At the end of the study, 81 of 100 users classed the Mirena® regimen as good or very good, while 74 of 100 users rated Trisequens® as good or very good. Long-term studies also show high rates of continuation; Hampton et al.136 reported continuation rates of 80 per 100 women at 60 cycles. Similarly, in another long-term follow-up study, 89% of the 40 post-menopausal women initiated on treatment with Mirena® plus continuous oral or transdermal E2 were still using Mirena® 5 years later.26

Although post-menopausal women often have a smaller uterus than peri-menopausal or younger women, insertion of Mirena® was easy in most studies with post-menopausal participants.26,71,73 In one 5-year prospective cohort study, the majority of women reported mild or no pain during the first insertion of Mirena® and during reinsertion of a new system after 5 years.26

A global analysis of tolerability compiled from published and unpublished studies of Mirena® in HRT identified headache, breast pain, abdominal pain, depression and nausea as the most common adverse effects. These were mostly mild, declined in incidence over time, occurred at similar rates as with comparator regimens and rarely led to discontinuation.

The use of Mirena® does not appear to counteract the favorable effects of ERT on the plasma lipid and lipoprotein profiles. Studies in women receiving estrogens plus Mirena® have generally shown neutral or beneficial effects (i.e. a reduction) on total cholesterol, total triglycerides and low-density lipoprotein cholesterol.61,139–141 Effects on high-density lipoprotein cholesterol and its subfractions have been more variable. Studies have recorded slight or transient reductions139,141 or no change.72 However, although these markers are considered good surrogates for the risk of cardiovascular disease, the role of HRT in preventing cardiovascular disease is controversial. As such, HRT should not be used for the primary or secondary prevention of cardiovascular disease.

Mirena® in combination with daily oral E2 does not appear to cause a marked effect on breast cell proliferation.142

8. PROTECTION FROM ENDOMETRIAL HYPERPLASIA DURING ERT
In general, women prefer HRT regimens that are associated with amenorrhea over sequential regimens that are associated with a monthly withdrawal bleed.143,144 The transition from using Mirena® as a reproductive-age contraceptive method to menopause-related endometrial protection during ERT was shown to have no adverse effects on the bleeding profile.145 Among the women who switched to ERT, the number of bleeding/spotting days decreased from 10 ± 13 days in the last contraceptive reference period to 9 ± 12 days in the first 90-day reference period of the ERT phase. In addition, continuing Mirena® from contraception to be part of HRT had a positive effect on quality of life.

Irregular bleeding and spotting have been reported to be particularly common among peri-menopausal women using continuous combined regimens.146 In two studies in peri-menopausal women using Mirena® with continuous HRT, 83%48 and 38%138 became amenorrheic by 1 year, and in the study by Boon et al.138 the rate of amenorrhea increased to 62% by year 2. In post-menopausal women using Mirena® with continuous HRT, amenorrhea rates ranged between 50% and 75% at 6 months, increasing to 64–90% at 1 year.26,72,135,137 These rates are comparable with those reported for oral continuous combined HRT regimens (Figure 22).71,146–152


As expected, bleeding or spotting was one of the most common reasons for discontinuing Mirena® among peri-menopausal women. Nevertheless, such discontinuations were infrequent within individual studies (even when irregular bleeding or spotting was noted),138 and generally occurred at a similar rate to, or less often than with comparator regimens.49,50,71,135,137,138 In particular, bleeding-related discontinuations were rare after the first 2 years of use.75,52

In summary, continuous combined HRT based on Mirena® produces a pattern of bleeding that is acceptable to most peri- and post-menopausal women.
9. References


2. Scholten PC. The levonorgestrel IUD: clinical performance and impact on menstruation University Hospital, Utrecht, 1989


8. Ortiz ME, Croxatto HB. The mode of action of IUDs. Contraception 1985;31:17–33


12. Mirena Expanded CCDS Bayer HealthCare Pharmaceuticals, Berlin, Germany. 22nd March 2011


1. NAME OF THE MEDICINAL PRODUCT
Mirena 20 microgrammes/24 hours intrauterine delivery system.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Levonorgestrel 52 mg. The initial release rate is 20 microgrammes/24 hours.

3. PHARMACEUTICAL FORM
Intrauterine delivery system (IUS).

Levonorgestrel (LNG) IUS consists of a white or almost white drug core covered with an opaque membrane, which is mounted on the vertical stem of a T-body. The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Removal threads are attached to the loop. The vertical stem of the IUS is loaded in the insertion tube at the tip of the inserter. The IUS and inserter are essentially free of visible impurities.

4. CLINICAL PARTICULARS
4.1 Indication(s)
Contraception
Idiopathic menorrhagia
Protection from endometrial hyperplasia during estrogen replacement therapy

4.2 Dosage and method of administration
4.2.1 Method of administration
Mirena is inserted into the uterine cavity and is effective for five years.

The in vivo dissolution rate is about 20 µg/24 hours initially and is reduced to about 10 µg/24 hours after five years. The mean dissolution rate of levonorgestrel is about 14 µg/24 hours over the time up to five years.

In women under hormonal replacement therapy, Mirena can be replaced by a new system at any time provided that there appears to be a menstrual cycle. If the system is removed in the mid-cycle and the woman has had intercourse within a week, she is at risk of pregnancy unless a new system is inserted immediately following removal.

After removal of Mirena, the system should be checked to be intact. During difficult removals, single cases have been reported of the whole cylinder sliding over the horizontal arms and hiding them together inside the cylinder. This situation does not require further intervention once completeness of the IUS has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

4.2.2 Instructions for use and handling
Mirena is supplied in a sterile pack which should not be opened until required for insertion. The exposed product should be handled with aseptic precautions. If use of the sterile package is broken, the product should be discarded.

4.3 Contraindications
Known or suspected pregnancy
Current or recurrent pelvic inflammatory disease
Lower genital tract infection
Postpartum endometritis
Infected abortion during the past three months
Cervicitis
Cervical displasia
Uterine or cervical malignancy
Prostaglandin-dependent tumors
Undiagnosed abnormal uterine bleeding
Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity
Conditions associated with increased susceptibility to infections
Acute liver disease or liver tumor
Hypersensitivity to the constituents of the preparation.

4.4 Special warnings and special precautions for use
Mirena may be used with caution after specialist consultation, or removal of the system should be considered if any of the following conditions exist or arise for the first time:
- migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia
- exceptionally severe headache
- jaundice
- marked increase of blood pressure
- severe arterial disease such as stroke or myocardial infarction

Mirena may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis. Antibiotic prophylaxis should be administered to these patients when inserting or removing the IUS.

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of Mirena.

Irregular bleedings may mask some symptoms and signs of endometrial polyps or cancer, and in these cases diagnostic measures have to be considered.

Mirena is not the method of first choice for young nulligravid women, nor for postmenopausal women with advanced uterine atrophy.

Due to the limited exposure in Mirena trials in the indication protection from endometrial hyperplasia during estrogen replacement therapy, the available data are not sufficient to confirm or refute a risk for breast cancer when Mirena is used in this indication.

Medical examination/consultation
Before insertion, the woman must be informed of the efficacy, risks and side effects of Mirena. A physical examination including pelvic examination, examination of the breasts, and a cervical smear should be performed. Pregnancy and sexually transmitted diseases should be excluded, and genital infections have to be successfully treated. The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of Mirena is particularly important in order to ensure uniform exposure of the endometrium to the progestogen; prevent expulsion and maximize efficacy. Therefore, the instructions for the insertion should be followed carefully. Insertion and removal may be associated with some pain and bleeding. The procedure may precipitate fainting as a vasovagal reaction, or a seizure in an epileptic patient.

The women should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

Mirena may not be suitable for use as a postpartum contraceptive.

Because irregular bleeding/spotting is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of Mirena.

If the woman continues the use of Mirena inserted earlier for contraception, endometrial pathology has to be excluded in case bleeding disturbances appear after commencement of estrogen replacement therapy.

If bleeding irregularities develop during a prolonged treatment, appropriate diagnostic measures should also be taken.

Oligo/amenorrhea
In women of fertile age, oligomenorrhea and amenorrhea develop gradually in 57% and 16% of women, respectively. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation.

When Mirena is used in combination with continuous estrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year.

Pelvic infection
Known risk factors for pelvic inflammatory disease are multiple sexual partners. Pelvic infection may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy.

If the woman experiences recurrent endometritis or pelvic infections or if an acute infection is severe or does not respond to treatment within a few days, Mirena must be removed.

Expulsion
Symptoms of the partial or complete expulsion of any IUD may include bleeding or pain. However, the system can be expelled from the uterine cavity without the woman noticing it leading to loss of contraceptive protection. Partial expulsion may decrease the effectiveness of Mirena. As Mirena decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion.

A displaced Mirena should be removed. A new system can be inserted at that time.

The woman should be advised how to check the threads of Mirena.

Perforation
Perforation or penetration of the uterine corpus or cervix by an intrauterine contraceptive may occur rarely, most often during insertion and may decrease the effectiveness of Mirena. Such a system must be removed. The risk of perforations may be increased in postpartum insertions (see 4.2 Dosage and method of administration), in lactating women, and in women with fixed retroverted uterus.
Ectopic pregnancy
Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry a higher risk of ectopic pregnancy. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain – especially in connection with missed periods or if an amenorrhic woman starts bleeding. The ectopic pregnancy rate with Mirena is approximately 0.1% per year. The absolute risk of ectopic pregnancy in Mirena users is low. However, when a woman becomes pregnant with Mirena in situ, the relative likelihood of ectopic pregnancy is increased.

Lost threads
If the retrieval threads are not visible at the cervix on follow-up examinations, pregnancy must be excluded. The threads may have been drawn up into the uterus or cervical canal and may reappear during the next menstrual period. If pregnancy has been excluded, the threads may usually be located by gently probing with a suitable instrument. If they cannot be found, the system may have been expelled. Ultrasound diagnosis may be used to ascertain the correct position of the system. If ultrasound is not available or unsuccessful, X-ray may be used to locate Mirena.

Ovarian cysts
Since the contraceptive effect of Mirena is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. Ovarian cysts have been reported as adverse drug reactions in approximately 7% of women. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases, the ovarian cysts disappear spontaneously during two to three months’ observation. Should this not happen, continued ultrasound monitoring and other diagnostic/therapeutic measures are recommended. Rarely, surgical intervention may be required.

4.5 Interaction with other medicinal products and other forms of interaction
The metabolism of progestagens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, such as antimetabolites (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nitisinone, efavirenz). The influence of these drugs on the efficacy of Mirena is not known, but it is not believed to be of major importance due to the local mechanism of action.

4.6 Pregnancy and lactation
4.6.1 Pregnancy
The use of Mirena during an existing or suspected pregnancy is contraindicated (see 4.3 Contraindications). If the woman becomes pregnant when using Mirena removal of the system is recommended, since any intra-uterine contraceptive left in situ may increase the risk of abortion and preterm labor. Removal of Mirena or probing of the uterus may result in spontaneous abortion. If the woman wishes to continue the pregnancy and the system cannot be withdrawn, she should be informed about the risks and the possible consequences of premature birth to the infant. The course of such a pregnancy should be closely monitored. Ectopic pregnancy should be excluded. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever. Because of the intrauterine administration and the local exposure to the hormone, the possible occurrence of visualizing effects in the fetus should be taken into consideration.

4.6.2 Lactation
About 0.1% of the levonorgestrel dose is transferred to the infant during breast-feeding. However, it is not likely that there will be a risk for the infant with the dose released from Mirena, when it is inserted in the uterine cavity. There appears to be no deleterious effect on infant growth or development when using Mirena after six weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk.

4.6.3 Fertility
Upon removal of Mirena, women return to their normal fertility.

4.7 Effects on ability to drive or use machines
Not known.

4.8 Undesirable effects
< For US see Appendix I >

4.8.1 Summary of the safety profile
The majority of women experience changes in menstrual bleeding pattern after insertion of Mirena. During the first 90 days, prolonged bleeding is experienced by 22% and irregular bleeding by 67% of women after postmenstrual insertion of Mirena, decreasing to 3% and 19% at the end of the first year of use, respectively. Concomitantly, amenorrhea is experienced by 0% and infrequent bleeding by 11% during the first 90 days, increasing to 16% and 57% at the end of the first year of use, respectively. When Mirena is used in combination with continuous estrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year.

4.8.2 Tabulated list of adverse reactions
The frequencies of adverse drug reactions (ADRs) reported with Mirena are summarized in the table on page 56.

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<td>Blood pressure increased</td>
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</tbody>
</table>

* Endometrial protection trials: “common”; ** Endometrial protection trials: “very common”

The frequencies of adverse drug reactions (ADRs) reported with Mirena are expressed as crude incidences of the events observed in clinical trials in the indication protection from endometrial hyperplasia during estrogen replacement therapy. Cases of breast cancer have been reported (frequency unknown, see Section 4.4 Special warnings and special precautions for use). The following ADRs have been reported in connection with the insertion or removal procedure of Mirena:

- Procedural pain
- Procedural bleeding
- Insertion-related vaso-ovagal reaction with dizziness or syncope
- The procedure may precipitate a seizure in an epileptic patient.

4.9 Overdose
Not relevant.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03BA03
Pharmacotherapeutic group: Plastic IUD with progestogen
Levonorgestrel is a progestogen with anti-estrogenic activity used in gynecology in various ways: as the progestogen component in oral contraceptives and in hormonal replacement therapy, or alone for contraception in progestogen-only pills and subdermal implants. Levonorgestrel can also be administered into the uterine cavity with an intrauterine delivery system. This allows a very low daily dosage, as the hormone is released directly into the target organ.

Mirena has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentration in the endometrium down-regulates endometrial estrogen and progesterone receptors, making the endometrium insensitive to the circulating estradiol and a strong anti-proliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction are observed during use of Mirena. Thickening of the cervical mucus prevents passage of the sperm through the cervical canal. The local influx of the uterus and of the ovarian tubes inhibits sperm mobility and function, preventing fertilization. Ovulation is inhibited in some women.

The contraceptive efficacy of Mirena has been studied in 5 major clinical studies with 3330 women using Mirena. The failure rate (Pearl Index) was approximately 0.2% at 5 years. The failure rate also includes pregnancies due to unintended sexual acts and pregnancies. Similar contraceptive efficacy has been observed in a large post-marketing study with more than 17000 women using Mirena.

5.2 Pharmacokinetic properties

Absorption

Following insertion Mirena releases levonorgestrel without delay. The high local drug exposure in the uterine cavity which is important for the local action of Mirena on the endometrium, leads to a strong concentration gradient via the endometrium to the myometrium (gradient endometrium to myometrium >100-fold), and to low concentrations of levonorgestrel in serum (gradient endometrium to serum >1000-fold). The in vivo release rate of levonorgestrel in the uterine cavity is initially approximately 20 μg/24 hours and declines to 10 μg/24 hours after 5 years.

Distribution

Levonorgestrel is bound non-specifically to serum albumin and specifically to sex-hormone-binding globulin (SHBG). About 1%–2% of the circulating levonorgestrel is present as free steroid and 42%–62% is specifically bound to SHBG. During the use of Mirena, the concentration of SHBG decreases. Accordingly, the fraction bound to SHBG decreases during the treatment and the free fraction increases. The mean apparent volume of distribution of levonorgestrel is about 106 L.

After insertion of Mirena, levonorgestrel is detectable in serum after 2 hour. The maximum concentration is reached within 2 weeks after insertion. In correspondence with the declining release rate, the median serum concentration of levonorgestrel declines from 206 pg/mL (25th to 75th percentiles: 101 pg/mL to 294 pg/mL) at 6 months to 194 pg/mL (146 mg/mL to 286 pg/mL) at 12 months, and to 131 pg/mL (113 pg/mL to 149 pg/mL) at 60 months in women of reproductive age weighing above 55 kg. Body weight and serum SHBG concentration have shown to affect systemic levonorgestrel concentration i.e. low body weight and/or a high SHBG level increase levonorgestrel concentration. In women of reproductive age with a low body weight (37 to 55 kg) the median serum concentration of levonorgestrel is about 1.5-fold higher.

In postmenopausal women using Mirena together with non-oral estrogen treatment, the median serum concentration of levonorgestrel declines from 257 pg/mL (25th to 75th percentiles: 186 pg/mL to 326 pg/mL) at 12 months to 149 pg/mL (122 pg/mL to 180 pg/mL) at 60 months.

When Mirena is used together with oral estrogen treatment, the serum levonorgestrel concentration at 12 months is increased to approx. 478 pg/mL (25th to 75th percentiles: 341 pg/mL to 655 pg/mL) due to the induction of SHBG by oral estrogen treatment.

Biotransformation

Levonorgestrel is extensively metabolized. The major metabolites in the plasma are the unconjugated and conjugated forms of 3α, 5p-tetrahydrolevonorgestrel. Based on in vitro and in vivo studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel, CYP2E1, CYP1B1 and CYP2C9 may also be involved, but to a smaller extent.

Elimination

The total clearance of levonorgestrel from plasma is approx. 1.0 ml/min/kg. Only trace amounts of levonorgestrel are excreted in unchanged form. The metabolites are excreted with the feces and urine at an excretion ratio of about 1. The excretion half-life which is mainly represented by metabolites, is about 1 day.

5.3 Preclinical safety data

The preclinical safety evaluation revealed no special hazard for humans based on studies of safety pharmacology, toxicity, genotoxicity, and carcinogenic potential of levonorgestrel. Levonorgestrel is a well-established progestogen. The safety profile following systemic administration is well documented. A study in monkeys with intravenous delivery of levonorgestrel for 12 months confirmed local pharmacological activity with good local tolerance and no signs of systemic toxicity. No embryo-toxicity was seen in the rabbit following intrauterine administration of levonorgestrel. The safety evaluation of the elastomer components of the hormone reservoir, polyethylene materials of the product, and combination of elastomer and levonorgestrel, based on both the assessment of genetic toxicity in standard in vitro and in vivo test systems and on biocompatibility tests in mice, guinea pigs, rabbits and in vitro test systems have not revealed bio-incompatibility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polydimethylsiloxane elastomer Silik, colloidal anhydrous Polyethylene Barium sulphate Iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Instructions for use/handling

See document “Insertion Instructions” Mirena/Intrauterine delivery system/CCDS/Version 14/22-March-2011
Insertion instruction

Mirena® 20 micrograms/24 hours intrauterine delivery system

To be inserted by a healthcare professional.

- Mirena® is supplied sterile.
- Mirena® is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the inner package is damaged or open. Insert before the month shown on the label.
- Mirena® is inserted with the provided inserter (Figure 1) into the uterine cavity within 7 days of the onset of menstruation or immediately after legal termination of pregnancy by carefully following the insertion instructions.
- It can be replaced by a new system at any time of the cycle.

Preparation for insertion

- Examine the woman to establish the size and position of the uterus to detect acute cervicitis or other genital contraindications and to exclude pregnancy.
- Visualize the cervix by means of a speculum and thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.
- Use an assistant as necessary.
- Grasp the upper lip of the cervix with a holding forceps. Gentle traction on the holding forceps has been shown to straighten the cervical canal. The forceps should remain in position throughout the insertion procedure to maintain gentle traction on the cervix against the pushing force of the insertion.
- Gently move a uterine sound across the uterine cavity to the fundus to determine the direction of the cervical canal and the depth of the uterine cavity (sound measure) and to exclude a uterine septum, synechiae and submucous fibroids. Should the cervical canal be too narrow, dilatation of the canal is recommended and consider the use of analgesics/paracervical block.

1. First open the sterile package completely (Figure 2a). Then use sterile gloves. Grab the shaft and rotate the inserter so that the centimeter scale marked on the insertion tube is upwards. Release the threads.
2. Holding the slider in the furthest position, pull on the threads (Figure 3a) to place the Mirena® system in the insertion tube. Note that the knobs at the ends of the arms now close the open end of the inserter (Figure 3b). If this does not happen, ensure that the arms will fold out horizontally by pulling the slider further back to the mark (Figure 7b). Align the open arms on a sterile surface as shown in Figure 2b, and return the slider into its furthest position.
3. Fix the threads in the cleft at the near end of the inserter shaft (Figure 4).

4. Set the flange as indicated in Figure 5.

5. Mirena® is now ready to be inserted. Continue to hold the slider with your forefinger or thumb firmly in the furthermost position.

6. Move the inserter carefully through the cervical canal into the uterus until the flange is situated at a distance of about 1.5–2 cm from the cervix to give sufficient space for the arms to open (Figure 6).

   **NOTE!** Do not force the inserter. Dilate the cervical canal, if necessary.

7. Push the inserter gently inwards until the flange touches the cervix. Mirena® should now be in the fundal position (Figure 8).

8. Holding the inserter firmly in position, release Mirena® by pulling the slider all the way down. The threads will be automatically released from the cleft (Figure 9). Before withdrawing the inserter, check that the threads are running freely.

9. Remove the inserter gently from the uterus. Cut the threads to leave about 2 cm visible outside the cervix (Figure 10).
IMPORTANT!
Should you suspect that the system is not in the correct position, check placement (e.g. with ultrasound).
Remove the system if it is not positioned completely in the uterine cavity. A removed system must not be re-inserted.

REMOVAL OF MIRENA®
Mirena® can be removed by pulling the threads with forceps.

SPECIAL NOTES
If pregnancy is not desired, the removal should be carried out during the menstruation in women of fertile age, provided that there appears to be a menstrual cycle. Otherwise contraception has to be ensured with other methods (e.g. condoms) starting at least 7 days before the removal. When the woman has no menses, she should also use barrier methods of contraception starting 7 days before removal and has to continue with this until her menstruation reappears.

After removal of Mirena®, the system should be checked to be intact. During difficult removals, single cases have been reported of the hormone cylinder sliding over the horizontal arms and hiding them together inside the cylinder. This situation does not require further intervention once completeness of the IUS has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

A new Mirena® can also be inserted immediately following removal, in which case no additional protection is needed.

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DATE OF REVISION OF THE TEXT:
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Mirena® EvolInserter™ insertion instructions
Quick reference guide for healthcare providers

1. First, open the sterile package completely (Figure 1). Then use sterile technique and sterile gloves.

2. Push the slider forward in the direction of the arrow to the furthest position to load Mirena® into the insertion tube (Figure 2).

   IMPORTANT! Do not pull the slider downwards as this may prematurely release Mirena®. Once released, Mirena® cannot be re-loaded.

3. Holding the slider in the furthest position, set the upper edge of the flange to correspond to the sound measurement of the uterine depth (Figure 3).

4. While holding the slider in the furthest position, advance the inserter through the cervix until the flange is approx. 1.5-2.0 cm from the uterine cervix (Figure 4).

   IMPORTANT! Do not force the inserter. Dilate the cervical canal, if necessary.

5. While holding the inserter steady, pull the slider to the mark to open the horizontal arms of Mirena® (Figure 5). Wait 5-10 seconds for the horizontal arms to open completely.

6. Advance the inserter gently towards the fundus of the uterus until the flange touches the cervix. Mirena® is now in the fundal position (Figure 6).

7. Holding the inserter in place, release Mirena® by pulling the slider all the way down (Figure 7). While holding the slider all the way down, gently remove the inserter by pulling it out. Cut the threads to leave about 2-3 cm visible outside of the cervix.

   IMPORTANT! Should you suspect that the system is not in the correct position, check placement (e.g., with ultrasound). Remove the system if it is not positioned properly within the uterine cavity. A removed system must not be re-inserted.

For complete insertion instructions, please consult the insertion instructions found in the Mirena® package.
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