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New Options in Contraception

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Introduction

In the last few years, more contraceptive options have been introduced into Canada, expanding choice for our patients. Patients and clinicians have experienced changes in how health care is accessed and delivered. For patients, this includes an increased use of the internet and social media as sources of information. Also included are changes to insurance coverage for contraception, such as provincial coverage for some (British Columbia, Quebec and Manitoba), and private insurance offered through school or an employer. In 2015 the cost of universal coverage of contraception in Canada was \$157 million, while the cost to provide health care for unintended pregnancies was \$320 million, providing a strong economic argument for this change.¹ For clinicians, the pandemic provided an opportunity for many to switch to increase the use of virtual care options, and toward efficiencies in practice.

Contraceptive consultation is generally focused on reaching shared goals of care with patients. While the immediate goal is to prevent pregnancy, the other goal is to prevent dissatisfaction and discontinuation of the method. Regarding the choice of contraceptive method, patients value choice, effectiveness, side effects, ease of use, as well as availability and cost,

interference with the sexual experience, and interaction with health care professionals.^{2,3} Best practice, therefore, requires that the clinician understands the priorities of the patient, including if or when pregnancy is desired, and also whether a long acting (clinician dependent) or a short acting (user dependent) method is preferred.

Updates on Long Term Reversible Contraceptives

When cost is not an option, over 75% of individuals opt for long-acting reversible contraception (LARC), strongly preferring the option of a very reliable method that does not require self-administration/application and that can be in place for 3 or more years.⁴ Evidence shows that discontinuation rates are significantly lower with LARC than with short acting reversible contraception.⁵ In particular, for teens aged 14–19 years, discontinuation is only 19% for LARC compared to 56% for short acting methods.⁶ It was estimated that if 10% of people in Canada switched from short term methods to LARC, health care savings would be approximately \$35 million annually in 2015, and the potential savings would likely be greater now.¹

Intrauterine Contraceptive	Duration of Use (Years)	COVID	Strength (mg/day LNG) (surface area of Cu)	Length (mm)	Width (mm)
LNG IUDs					
Kyleena (LNGIUS 12)	5	5	9 average mcg/day	30	28
Mirena (LNGIUS 20)	5	7	14 average mcg/day	32	32
Copper IUDs					
Flexis-T 300	5	5	300mm ²	28	23
Flexis-T 300+	5	5	300mm ²	32	28
Flexis-T 380+ (sleeves)	5 (12)	12	380mm ²	32	28
Liberte UT 380 Standard	5	7	380mm ²	35.4	32
Liberte UT 380 Short	5	7	380mm ²	28.4	32
Liberte TT 380 Standard (cuffs)	10 (12)	12	380mm ²	34	29.9
Liberte TT 380 Short (sleeves)	5	12	380mm ²	29.5	23.2
Mona Lisa 10 (sleeves)	10 (12)	12	380mm ²	35.85	31.85
Mona Lisa 5 Standard	5	7	380mm ²	31.9	31.8
Mona Lisa N (ST 300)	3 (5)	5	300mm ²	29	23
Mona Lisa 5 Mini (380)	5	7	380mm ²	24	30

Table 1. Canadian Intrauterine Contraceptives. Sizes of each IUD available in Canada, with the additional blue column showing a summary of the SOGC 2020 Guidance Document for duration of use.¹²

Today in Canada, the LARC family includes 11 copper intrauterine devices (IUDs), approved for 3 to 10 years of use depending on the type, and two levonorgestrel intrauterine systems (IUS), approved for 5 to 8 years. In 2020, the 3-year single rod sub-dermal implant (SDI) was approved for use in Canada. With the addition of this implant, choosing a LARC will depend on the bleeding profile and the desired location of the implant. LARC methods are highly effective and require a trained clinician for their insertion and removal. As such, they are sometimes termed a “set and forget” option.⁷ There is also evidence that the use of methods such as IUD and IUS reduce the risk of endometrial cancer.⁸

1) Copper IUD

The copper IUD is the most effective non-hormonal method of contraception. A patient

may strongly consider a copper IUD if they prefer not to use any hormones, owing to either prior poor experiences, personal preference, or a desire to be more aware of their inherent biological rhythm. They also may prefer to have a monthly menstrual cycle that is not induced by medication yet have the benefit of a LARC.

In Canada 11 distinct types of copper IUDs have regulatory approval, requiring one of three insertion methods. Sizes differ slightly, as well as the approved duration of use as illustrated in **Table 1**. Choosing which copper IUD to use is often a clinician preference based on the familiarity with one particular insertion method; however, there is strong evidence for the use of a smaller frame copper IUD for nulliparous patients. A large trial that included 927 nulliparous participants compared their experience with 2 IUDs: a 24 mm x 30 mm device or a

32 mm x 36 mm device. The study demonstrated that those who received the smaller frame copper IUD had significantly less bleeding, pain and expulsion.⁹ This trial's findings underscore the necessity that clinicians become familiar with all insertion techniques because pelvic pain and bleeding are common reasons for discontinuation of a copper IUD. Clinicians can play a role to minimize these issues, by selecting the appropriate type of copper IUD and by addressing myths and misconceptions.¹⁰

2) Levonorgestrel IUS

Many patients seek a reduction or elimination of bleeding in addition to the longer term and superior efficacy of the IUD, and this is accomplished with the addition of levonorgestrel (LNG) in various doses. While products with three different doses of LNG have been approved, only two are currently available in Canada. These include the LNG 19.5mg (containing 19.5 mg of LNG that releases 12 µg /24 hours) and the LNG-IUS 52mg (containing 52 mg of LNG that releases 20 µg /24 hours). Notably, there is currently no generic LNG IUS available in Canada. The LNG-IUS devices work by releasing LNG, a type of progestin, into the uterus, which allows for thickening of the mucous in the cervix, thus preventing sperm from penetrating. Ovulation is generally not suppressed. The implication of this is that some patients will occasionally notice cyclical changes at the time of ovulation. Return to fertility with discontinuation of this method is therefore immediate.

The LNG-IUS 19.5 mg is designed with a slightly smaller plastic frame as noted in **Table 1** and has a small silver ring at the cross junction of the T shape. This design allows for more accurate detection and localization by ultrasound. The LNG-IUS 19.5 mg is approved for use of up to 5 years, and there is no evidence for extended use beyond that time period. Those considering use of the LNG IUS 19.5 mg should be aware of possible irregular spotting, and/or small withdrawal bleeding.

The LNG-IUS 52 mg has been available for a longer period of time compared with the other LNG-IUS devices. The relative bleeding suppression achieved by each LNG-IUS over a 2 year period is illustrated in **Figure 1**. Since 2021, in Canada, the LNG-IUS 52 mg has been indicated for the treatment of idiopathic menorrhagia following an appropriate diagnostic investigation in women who accept the contraceptive effects.¹¹

Endometrial biopsy, if required, can be performed with the LNG-IUS in situ.

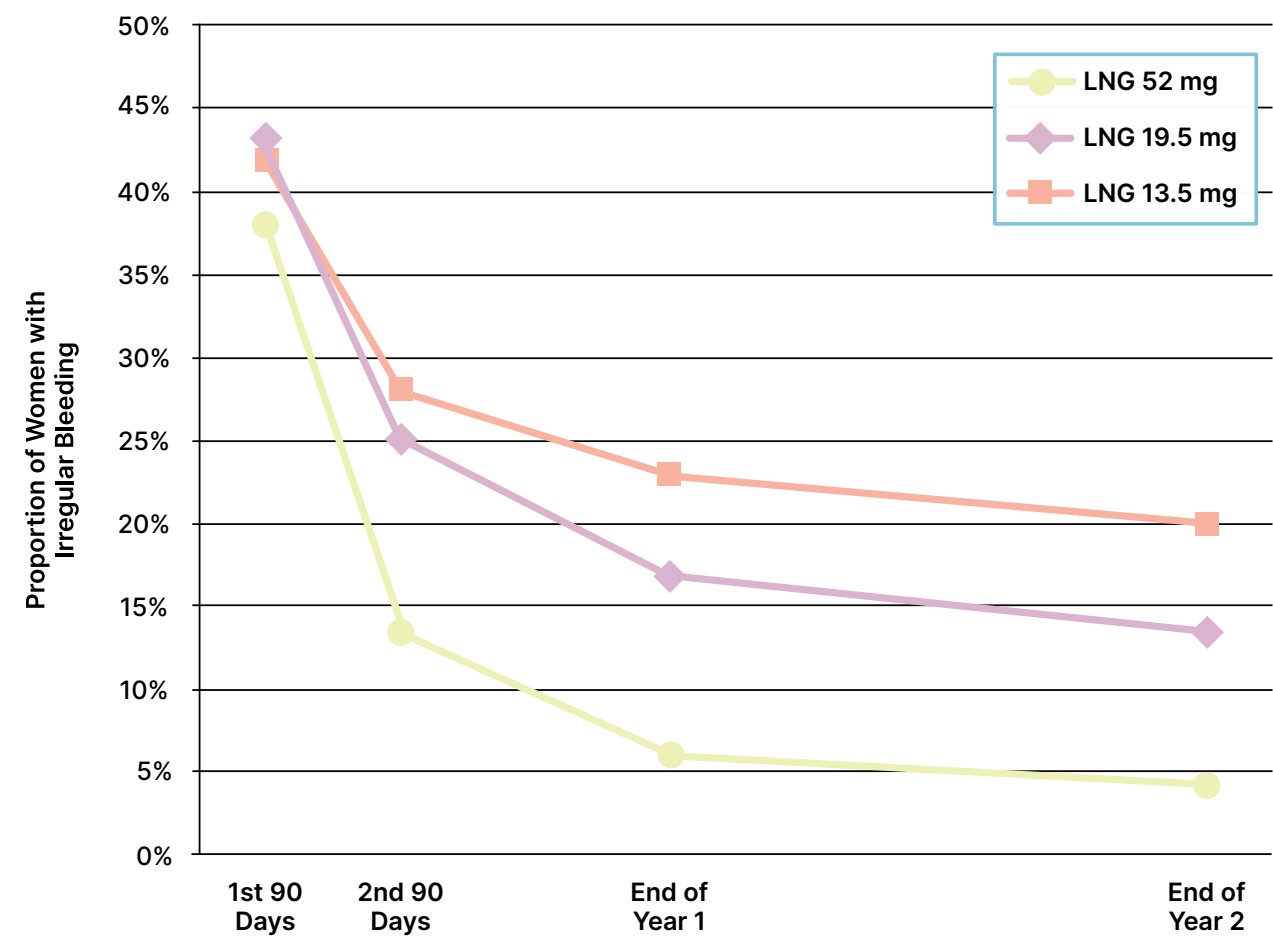
There is good evidence supporting some off label uses of the LNG-IUS 52 mg. For example, during the pandemic, several studies were conducted that reviewed the clinical use of both the copper IUD and the LNG-IUS 52 mg. These studies confirmed that the copper IUD and the LNG-IUS 52 mg can be safely used beyond the time approved. The Society of Obstetricians and Gynecologists of Canada Guidance Document supports use of the LNG-IUS 52 mg up to 7 years.¹² These off label but evidence based guidelines are illustrated in a separate column in **Table 1**. Another off label use of the LNG-IUS 52 mg includes use within 5 days as a post coital contraceptive with a success rate equivalent to the use of a copper IUD. In the randomized non-inferiority trial that included 317 participants who received an LNG-IUS 52 mg and 321 participants who received a copper T380A, only one pregnancy occurred.¹³ These findings offer reassurance for clinicians about both the timing of insertion and use of the LNG-IUS 52 mg.

Clinicians will be reassured to know that on February 18, 2024, Health Canada approved the LNG-IUS 52 mg for 8 years for contraception¹⁴, supporting previous findings and recommendations.

3) Subdermal Implant

As of September 2020, patients in Canada have access to the subdermal implant (SDI) as an additional contraceptive option. By December 2021, 2740 clinicians in Canada had been effectively trained in its insertion and removal via a virtual simulation-based training program.¹⁵ Patients can consult their clinician with the aim of having a longer-term contraception method that does not involve undressing or a vaginal examination. They may want a method that suppresses their menstrual period and is safe, especially if fertility in the future is a consideration.¹⁶

The SDI is effective for 3 years and has a Pearl Index slightly superior to that of the LNG-IUS, and even to that of tubal ligation or vasectomy.¹⁷ The SDI contains etonogestrel, which is an active metabolite of desogestrel. The contraceptive effect of etonogestrel is through inhibition of ovulation, though it also causes changes in the cervical mucus. The etonogestrel in the SDI is encapsulated in ethylene vinyl acetate and is impregnated with barium sulphate so that



LNG-IUS type	1st 90 days	2nd (90 Days)	End of Year 1	End of Year 2
LNG-IUS 52 mg	648 (38.1%) [n=1700]	220 (13.6%) [n=1621]	89 (6.1%) [n=1448]	52 (4.4%) [n=1178]
LNG-IUS 19.5 mg	665 (42.5%) [n=1566]	377 (25.0%) [n=1511]	226 (16.5%) [n=1371]	(14%)
LNG-13.5 mg*	643 (42.0%) [n=1531]	415 (28.1%) [n=1475]	300 (22.6%) [n=1329]	(20%)
p-values				
52 mg vs 19.5 mg	0.01	<0.0001	<0.0001	--
52 mg vs 13.5 mg	0.03	<0.0001	<0.0001	--
19.5 mg vs 13.5 mg	0.8	0.051	<0.0001	--

Figure 1. Relative bleeding suppression achieved by each LNG-IUS; *adapted from Goldthwaite et al, 2019.*

it is radio-opaque.¹⁸ This means that any imaging modality will be able to identify it, especially in the instances in which the implant is embedded too deeply and must be located prior to removal. In general, imaging is not needed, because the rod is superficially identified immediately after insertion and prior to removal/replacement by palpation and is typically located over the triceps muscle of the non-dominant arm.

While the effectiveness and insertion procedure of the SDI are appealing, patients should be advised that the likelihood of irregular bleeding is higher compared with any of the LNG-IUS devices. There are few direct comparison studies between the SDI and the LNG-IUS. For instance, a large study conducted in 38 centres in 6 countries enrolled 766 patients to compare their 12-month experiences with the SDI and the LNG-IUS 8 (containing 13.5mg of LNG that releases 8 µg /24 hours).¹⁹ Note that the LNG-IUS 8 is no longer available in Canada; however, what the report concludes is that 12-month discontinuation rates were 26.8% in the SDI group compared with 19.6% in the LNG-IUS 8 group, mainly because of increased irregular bleeding patterns. The relative suppression of bleeding between the etonogestrel implant (ENG) and the LNG-8 at each 90 day interval is illustrated in **Figure 2**.

Clinicians considering adding the SDI to their practice will find the insertion process similar to other dermatological procedures. The implant comes contained in an insertion device; however, clinicians need to prepare by landmarking the area and injecting local anesthetic. Following insertion, the site must be covered with a band aid or steri strips and pressure dressing applied. Removal of the device can be slightly more challenging than insertion, requiring a 2 mm incision to access the device and slide it out. This is then closed with steri strips. Removal of deeply embedded and non-palpable implants (which occur in 1% of patients) should not be attempted in the office; rather, consultation with experts is prudent.¹⁸

A 2-rod SDI is available in some countries that uses levonorgestrel rather than etonogestrel as the type of progesterone. These are non-radio opaque rods and can be left in place for 5 years, rather than 3 years. The insertion device is different, and while clinicians in Canada are not likely to insert a device that is not approved, they may be required to remove the device. Once the device is removed, the return to fertility is

rapid, thus patients can be advised that within 24 hours, fertility returns to baseline. Implants can, however, be used back-to-back, indefinitely.

Updates in Short Term Reversible Contraception

1) New Progesterone Only Pill

Progesterone-only pills (POP) are considered safe and can be appropriately prescribed in a virtual health consultation with minimal risk. The contraindications for POPs are limited and rare. International medical eligibility criteria can be consulted to verify the contraindications.²⁰ The contraindications include personal history of breast cancer, malabsorptive bariatric procedures, hepatocellular adenoma, and systemic lupus erythematosus with positive antiphospholipid antibodies, as well as ischemic heart disease or stroke. Those taking medications such as certain anticonvulsants or rifampin should neither initiate nor continue taking a POP. However, POPs are appropriate for most people, particularly those who have contraindications to the use of estrogen, such as people with hypertension, those who do not tolerate estrogen, smokers over the age of 35, or those who are breastfeeding exclusively.

For many years, the POP available in Canada contained 0.35 mg daily of norethindrone, which works primarily by thickening the cervical mucus to inhibit sperm penetration. Norethindrone also lowers the midcycle LH and FSH peaks, slows the movement of the ovum through the fallopian tubes, and alters the endometrium with suppression of ovulation in approximately half of users.²¹ For patients, the benefit of taking a POP is reduction in bleeding and suppression or elimination of menstrual periods. While this POP is effective for contraception, it has a short half life, and therefore must be taken every 24 hours. The clinical guidelines for POPs that indicate a “three-hour window” of tolerance before back-up contraception should be used have been recently reviewed.²² These guidelines are primarily based on one study that Cox et al. conducted in 1968 that included 6 women using megestrol acetate (0.5 mg), which is a progestin no longer sold as an oral contraceptive for humans.²³ The study found that megestrol acetate did not lead to any ovulation suppression. The median Pearl index for most POPs is higher than for combined oral contraceptive pills (COCP), which means that there is generally a higher risk of pregnancy.

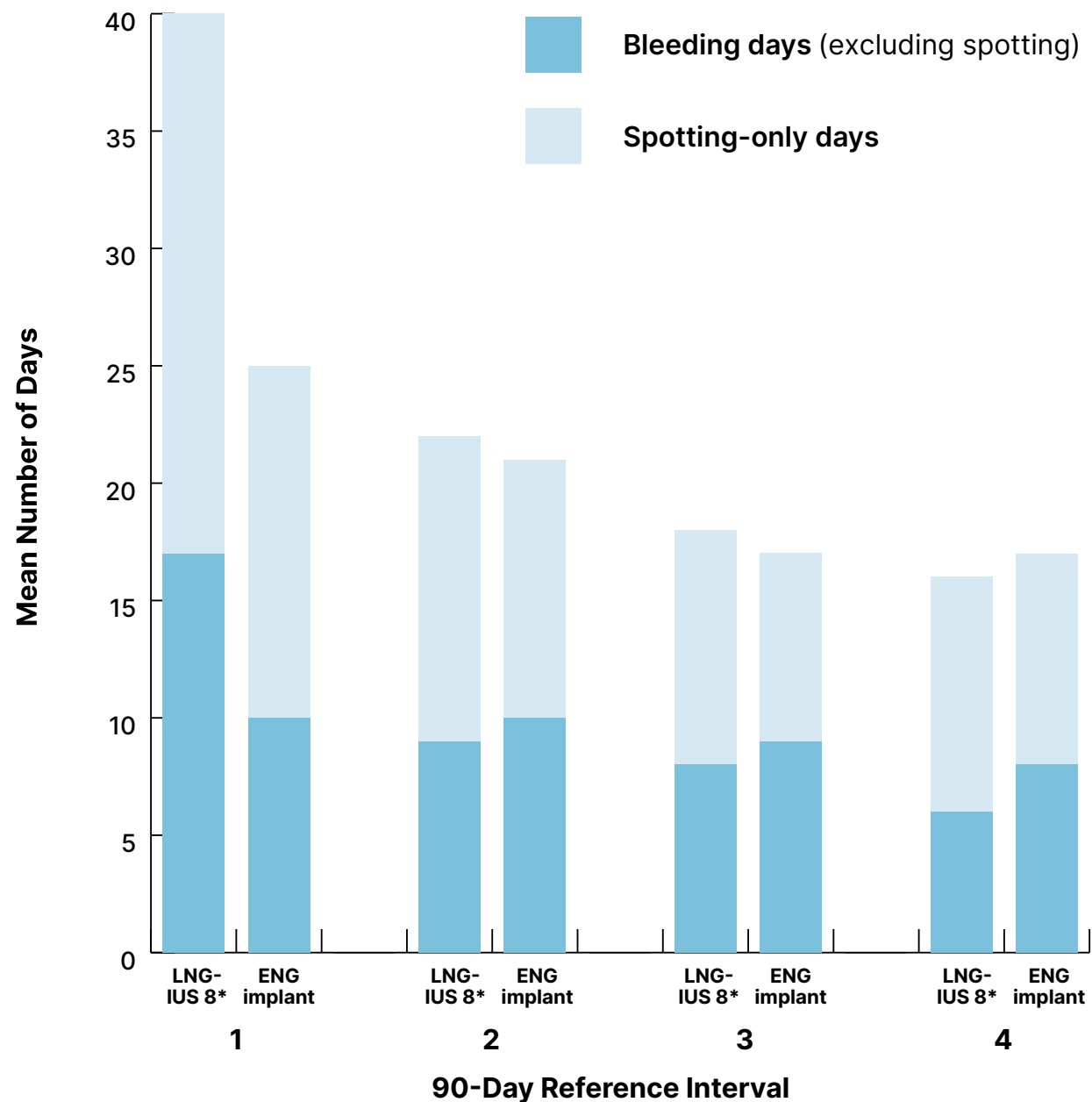


Figure 2. Relative suppression of bleeding between the etonogestrel implant (ENG) and the LNG-8, which is no longer available in Canada; *adapted from Apter et al, 2016.*

Mean number of bleeding and spotting days by 90-day reference intervals (modified intention-to treat set) in the LNG-IUS 8 and ENG implant groups. The numbers of bleeding and spotting days were not recorded at baseline. Modified intention-to-treat set: all women for whom at least one placement/insertion attempt was made. ENG = etonogestrel; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 µg/24 hours during the first year).

Abbreviations: LNG-IUS: levonorgestrel intrauterine system; ENG: etonogestrel

*LNG-IUS 8, marketed as *Jaydess*, is no longer available in Canada.

However, a new POP is as effective as COCPs, and has an equivalent Pearl Index. This POP was recently approved in Canada and contains a different progestin (4 mg of drospirenone) that has a long half life. This POP is packaged with 24 active treatment days followed by 4 placebo tablets. The primary mechanism of action is suppression of ovulation, and in studies,²⁴ despite the 4-day hormone-free period and multiple intentional 24-hour delays in tablet intake, ovulation inhibition was maintained. This option should be considered for most patients desiring or requiring a POP.

2) New Considerations in Combined Oral Estrogen and Progesterone Pills

Many patients do well on a COCP, because the addition of estrogen to the progestin base allows the lining of the uterus to thicken and stabilize, leading to a more regulated and predictable withdrawal bleed, (or menstrual period), when the estrogen is discontinued for a few days. Estrogens reduce both follicle development and secretion of FSH, leading to ovulation inhibition. Various products have adjusted both the amount and duration of the estrogen contained in the COCP to address the reasons for discontinuation. Until recently, the only estrogen available in COCPs in Canada has been ethinyl estradiol, which is metabolized by the cells and has systemic effects on the bone, breast and uterus—all organs that have estrogen receptors. COCPs available in Canada contain different types and quantities of progestins.

Patients may experience challenges finding a suitable COCP with no side effects, such as unwanted bleeding, spotting or break-through-bleeding, or adverse impacts on mood. For example, satisfaction rates with COCP use can be as low as 55%.²⁵ However, clinicians may be less aware of this because discontinuation of any pill does not require a clinical visit. Patients may subsequently seek medical attention for a pregnancy termination, or with a mis-timed pregnancy, or for the use of over-the-counter agents such as the morning after pill. Adjusting the amount of ethinyl estradiol from 10 mcg to 35 mcg has been one option to address the side effects of bleeding.

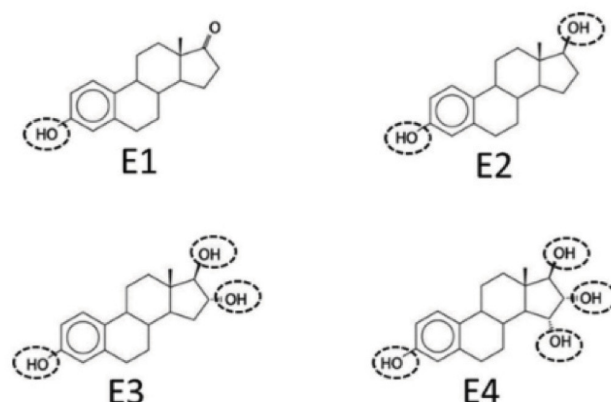


Figure 3. Comparison of naturally occurring estrogens. Molecular structures of estrone (E1), estradiol (E2), estriol (E3) and estetrol (E4). The dashed line circles depict -OH groups; adapted from Grandi et al, 2020.

The novel estrogen, estetrol (E4), recently approved in Canada, is a promising alternative for patients because of its tolerability and safety profile.²⁶ E4 is a naturally occurring estrogen and is an estrogen with selective activity in tissues. **Figure 3**²⁷ shows the chemical configuration of all four naturally occurring estrogens. It has minimal impact on triglycerides and breast stimulation, and has minimal impact on hepatic metabolism, while continuing to have estrogenic effects on the uterovaginal tissues, bone and brain. E4 is made from a plant source, which may be important to some patients. It occurs naturally in the human body, during fetal development.

A trial looked at COCPs that combined E4 with both LNG and drospirenone at various doses to optimize bleeding patterns, cycle control, and satisfaction.²⁸ As a result, the optimum combination was found to be drospirenone at a dose of 3 mg, administered in a regimen of 24 active days followed by 4 inactive days. The trials have shown a statistically significant improvement in favourable bleeding patterns, high levels of user acceptability, and effective control of body weight. Long term results regarding venous thromboembolism risk are being tracked; although initial clinical results suggest a lower rate of VTE, this needs to be confirmed with larger studies. Therefore, at present, clinicians should follow established contraindications for COCPs when recommending this new option to patients.²⁹

Conclusion

Selecting a contraceptive method requires increasingly focused discussions to establish reproductive health goals and to consider broader health care considerations. Patients are equal partners in collating relevant information for decision making. In the last few years, the introduction of additional information and products for both long-term and short-term contraceptive use has expanded options, and improved safety. There is reason for optimism that there will be a reduction in the burden and cost of unplanned pregnancies. Crucially, universal coverage of contraception will allow patient choice to become a reality in Canada.

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