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“Seek simplicity, and mistrust it.”
Alfred North Whitehead
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### Definitions and Abbreviations

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<tr>
<td>ACOG</td>
<td>American Congress of Obstetricians and Gynecologists</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CHC</td>
<td>Combined hormonal contraceptive (oral, patch, ring)</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>COC</td>
<td>Combined oral contraceptive (EE &lt; 50 mcg + progestin combinations)</td>
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<tr>
<td>DMPA</td>
<td>Depot medroxyprogesterone acetate</td>
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<tr>
<td>EC</td>
<td>Emergency contraception</td>
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<tr>
<td>EE</td>
<td>Ethinyl estradiol</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>IUD</td>
<td>Intrauterine device</td>
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<tr>
<td>LN/LNG</td>
<td>Levonorgestrel</td>
</tr>
<tr>
<td>NA</td>
<td>Norethindrone acetate</td>
</tr>
<tr>
<td>OC</td>
<td>Oral contraceptive</td>
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<tr>
<td>POP</td>
<td>Progestin only pill</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SOGC</td>
<td>Society of Obstetricians and Gynecologists of Canada</td>
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<tr>
<td>STD</td>
<td>Sexually transmitted disease</td>
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<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Summary

The objective of this Academic Detailing Session is to provide practitioners with up-to-date, relevant information on strategies to prevent unintended pregnancies.

- **Removing unnecessary barriers** can help patients access and be successful with their contraception.
- The recommendations derived from the Centers for Disease Control and Prevention (CDC) guidelines referred to in this document apply to healthy women.
- **Medical Eligibility Charts** have been developed by the World Health Organization (WHO) and adapted by others and are a tool to help determine the most appropriate choice of contraception for women with known medical conditions. (See Appendix 3)
- A medical and drug history to assess medical eligibility for combined hormonal contraception should be conducted to rule out contraindications or potential drug interactions.
- A medical history can accurately determine when a woman is not pregnant (see Appendix 1).
- Routine pregnancy tests for every woman are not necessary and should be based on clinical judgement, keeping in mind that test accuracy is dependent on several factors including recent sexual intercourse or early pregnancy.

**Question 1: What are the clinical considerations for healthy women requesting contraception?**

**Age**

- The risk of cardiovascular disease increases with age and may also increase with combined hormonal contraceptive use. In non-smokers and the absence of other adverse clinical conditions, guidelines suggest that combined hormonal contraceptives can be used until menopause, aged 50-55, although evidence is lacking in this age group.
- **Combined** hormonal contraceptive is not recommended in women > 35 years of age who are smokers.
- The recommendations in CDC guidelines apply to all healthy women including adolescents.

**Increased Weight or Obesity**

- A 2013 Cochrane Review reported that in 13 studies (N=49,712), there was generally no evidence that BMI affected combined hormonal contraceptive efficacy.
  - The authors caution there was limited evidence for any individual contraceptive method and the overall quality of evidence was low.

**Acne Indication**

- Products approved for only acne, and those approved for both acne and contraception are listed in the table in Appendix 2 and on the laminate.
A 2012 Cochrane Review reported:

- Of 9 placebo-controlled trials with data for analysis, all showed COCs reduced acne lesion counts, severity grades and self-assessed acne compared to placebo; and
- Few important and consistent differences between COC types in their effectiveness for treating acne, although products containing cyproterone seem to improve acne better than those containing levonorgestrel. This conclusion is based on limited evidence.

**Smoking**

- Combined estrogen/progestin hormonal contraception is **not recommended** in women over 35 years of age who smoke.
- In women < 35 who smoke, advantages of combined estrogen/progestin generally outweigh risk but are not considered a choice without restrictions.

**Migraine**

- The majority of guidelines state that contraceptive estrogen/progestin combinations should not be used in women of any age who experience migraines with aura, as there is an unacceptable increased risk for stroke. While the absolute risk may be small, the effects can be devastating, especially considering that alternative methods of contraception are available.
- In women with migraine **without aura** who are age > 35 years, combined estrogen/progestin contraception is not usually recommended unless other more appropriate methods are not available or not acceptable.
- In women with migraine **without aura** < 35 years of age, combined estrogen/progestin contraception is considered to have advantages that outweigh theoretical or proven risks.
- According to the Medical Eligibility Charts (Appendix 3), copper IUDs have no restrictions on use in patients with migraine with aura while for progestin only contraceptives (oral or IUD), it is considered that the advantages generally outweigh theoretical or proven risks.

**Question 2: What is the comparative effectiveness of contraceptive methods?**

- The Pearl Index (number of pregnancies per 100 woman years) is a common measure used to summarize contraceptive effectiveness.
- The reported failure rate of oral contraceptives is generally the same, approximately 9% with usual use and 0.3% with perfect use.
- Nine out of 100 women become pregnant with usual use of COCs or progestin only pills in the first year.
- IUD’s offer enhanced efficacy rates with failure reported as 0.2%, as compliance is not a factor.
- Consistent and correct use of male latex condoms are required to reduce the risk of STDs, including HIV.
- A medical and drug history to assess medical eligibility for CHC should be conducted to rule out contraindications or potential drug interactions.
Among healthy women, few examinations or tests are needed before initiation of contraceptives:

- Blood pressure assessment prior to initiation of combined hormonal contraception is considered essential and mandatory in all circumstances for safe and effective use; and
- Bimanual examination and cervical inspection are required prior to insertion of IUDs.

Van Vleit and colleagues performed Cochrane Reviews investigating differences between multiphasic and monophasic approaches.

- The reviews generally conclude there is insufficient evidence to make comparisons between multiphasic products.
- Monophasic pills should be the first choice for women starting oral contraceptive use.
- High quality comparative data on which to base conclusions are limited.

Extended or continuous regimens have similar pregnancy rates and safety profiles as 28-day regimens.

Factors affecting the efficacy of oral contraceptive methods include:

- Non-compliance (late or missed pills) - of note, progestin only pills are less tolerant of non-adherence as a dose is considered missed if it is > 3 hours from when it should have been taken;
- Vomiting or diarrhea for any reason;
- Clinically significant drug interactions.

Question 3: What are the special circumstances or risks when choosing a contraceptive method?

- Postpartum and Breastfeeding Considerations
  - If < 21 days postpartum, there is some theoretical concern regarding the association between combined hormonal contraceptive use and the risk of thrombosis in the mother. Blood coagulation and fibrinolysis are essentially normalized by three weeks postpartum.
  - For women who are medically eligible, delay starting CHCs until 4 weeks if breastfeeding and 6 weeks if the woman has other risk factors for VTE.
  - Most trials in a recent Cochrane Review did not report significant differences between study arms in breastfeeding duration, breast milk composition, or infant growth in women using hormonal contraception.

- Venous Thromboembolic Events (VTEs)
  - The risk for VTE is higher in women taking combined oral contraceptives than in those who do not; however the absolute risk is low and substantially less than during pregnancy or the postpartum period. It has been estimated that 2000 women would need to switch to a low risk combined oral contraceptive to prevent 1 VTE per year.
The risk of VTE in COC users is highest in the first months of use, falling towards baseline thereafter. Pill breaks should be discouraged as the elevated risk may occur when COCs are re-initiated.

Research demonstrates that COCs with estrogen in daily doses ≤ 35 mcg EE carry a lower risk of VTE than those with 50 mcg EE. There are insufficient data to suggest progressively lower risk with EE less than 35 mcg.

There are conflicting data and therefore uncertainty on whether risks differ due to the type of progestin.

- Epidemiological studies tend to report an increased risk with drospirenone and cyproterone.
  - Epidemiological studies may not control for other risk factors such as age, obesity, smoking, family history, etc.
- Prospectively designed studies tend to report no increased risk between different progestins.

Cyproterone (e.g., Diane 35®, Cyestra®, etc.) product information carries a warning that it appears to have an elevated risk of venous thromboembolic events compared to users of levonorgestrel-containing combined oral contraceptives.

Drospirenone (e.g., Yaz®, Yasmin®, etc.) product information instructs prescribers to consider the benefits and risks with respect to VTE risk given the current retrospective epidemiological studies suggesting a higher risk of VTE compared to levonorgestrel-containing COCs.

Healthcare providers should consider a woman’s current risk factors and re-assess risk over time. Patients should be counselled on the signs and symptoms of VTE when prescribed a CHC.

Progestin only contraception (e.g., Micronor®, Mirena®, Depo-Provera®) carries no apparent increased risk of VTE or stroke.

The Academic Detailing Service agrees with recommendations that, given the uncertainty, it seems reasonable to prescribe COCs containing progestins with potentially lower risk of VTE such as levonorgestrel or norethindrone as first choice. In women who are already at increased risk due to existing risk factors for VTE, prescribing a progestin only preparation is preferable.

Risk of Stroke

According to the American Heart Association:

- Combined oral contraceptives increase the risk of stroke approximately twofold over non-users.
  - The majority of evidence is from cohort or case control studies and primarily refers to ischemic strokes.
  - Evidence for increased risk of hemorrhagic strokes is less consistent.
The risk of stroke is very low in the age group of women who use contraception, but the incidence rises steeply from 3.4 per 100,000 at ages 15 to 19 years to 64.4 per 100,000 in women aged 45 to 49 years.

Subgroups of women may be at higher risk for stroke, including women who are older, smoke cigarettes, have hypertension, diabetes, obesity, hypercholesterolemia, and prothrombotic mutations.

The American Heart Association guidelines advocate for blood pressure evaluation prior to hormonal contraceptive initiation, as well as, the treatment of stroke risk factors among oral contraceptive users.

To put this into perspective, stroke rates are higher in pregnant than non-pregnant women (34 vs. 21 per 100,000), with the highest risk in the third trimester and postpartum.

**Bone Mineral Density**

Hormonal contraceptive use has been associated with changes in bone mineral density but it is not clear whether there is an increase (i.e., DMPA, Depo-Provera®) or a decrease (with estrogen containing contraceptives) in the risk of fractures later in life.

Short or long-term use of DMPA in healthy women should not be considered an indication for dual-energy X-ray absorptiometry (DXA) or other tests that assess bone mineral density.

In adolescents, the advantages of DMPA likely outweigh the theoretical safety concerns regarding bone mineral density and fractures. However, in the absence of long-term data in this population, consideration of long-term use should be individualized.

**Perimenopausal Considerations**

The median age of menopause is 51 years but can vary from ages 40 to 60.

The progestin only pill and IUD can be used by women until menopause.

Combined oral contraceptives may have some benefits in perimenopausal women on bone mineral density and vasomotor symptoms; as well as, the reduced risk in ovarian and endometrial cancers. However these benefits must be weighed against age-related increases in obesity and risk for cardiovascular disease, such as VTE.

**Question 4: What are the regimens to use when emergency contraception is needed?**

The World Health Organization reports a pregnancy rate of 1.1% with the levonorgestrel-only regimen (e.g. Plan B) compared with 3.2% for the Yuzpe regimen (estrogen/progestin pills) - see table 5.

Effectiveness of EC declines with increasing delay of treatment following unprotected sexual intercourse.
Levonorgesterol (e.g. Plan B) prevents 95% of pregnancies when taken ≤ 24 hours after intercourse, 85% within 25 to 48 hours, and 58% within 49 to 72 hours. This is available in pharmacies without a prescription.

Corresponding figures for the Yuzpe regimen are 77%, 36%, and 31%.

The copper IUD is more effective than either the levonorgestrel or Yuzpe methods of emergency contraception.

Health Canada has issued warnings that emergency contraception is less effective in women with increased BMI. However, the effect of weight on the efficacy of EC is considered an area of uncertainty, and groups such as the SOGC, the European Medicine Agency and the Faculty of Sexual and Reproductive Health suggest obese women can use all methods of EC.

**Question 5: Is there evidence for other non-contraception benefits or harms of combined hormonal contraceptives?**

- There are non-contraceptive benefits to CHC, including cycle regulation and decreased dysmenorrhea and menstrual flow.

- Use of CHCs has been associated with a decreased risk of ovarian, endometrial and colorectal cancer, and an increased risk of breast and cervical cancer.
Introduction

The objective of this Academic Detailing Session is to provide practitioners with up-to-date, relevant information on strategies to prevent unintended pregnancy.

➢ Why is this important?
  o Many effective contraceptive methods are available in Canada. However, unintended pregnancies still occur and, in fact, 27% of respondents in a 2008 national survey reported having had an unplanned pregnancy.\(^1\)
  o From 2001 to 2010, the Canadian teen pregnancy rate (ages 15-19) declined by 20.3%.
    - However, the rate in Nova Scotia increased by 12.8%, primarily influenced by increasing rates between 2006 and 2010.\(^2\)

➢ Removing unnecessary barriers can help patients access and be successful with their contraception.\(^3\)

Who does this information apply to?\(^3\)

➢ The general recommendations developed by National and International Guidelines apply to persons who are presumed to be healthy.

➢ Known Medical Problems
  o If there are known medical problems or other special conditions, women may need additional examinations or tests before choosing the appropriate method of contraception.
  o Medical Eligibility Charts have been developed by the World Health Organization and adapted by others:
    - World Health Organization, 2009
      http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf?ua=1
    - U.S. Medical Eligibility Criteria for Contraceptive Use, 2010 CDC
      - Endorsed by ACOG.
    - Reproductive Health Access have developed a simplified version (See Appendix 3)
      http://reproductive-health-access-project-store.myshopify.com/products/medical-eligibility-for-initiating-contraception

➢ Contraceptive methods are rated on a scale of 1-4 (Appendix 3):
  1. Method can be used without restriction
  2. Advantages generally outweigh theoretical or proven risks
  3. Method not generally recommended unless other more appropriate methods are not available or not acceptable
  4. Method not to be used

➢ A medical and drug history to assess medical eligibility for combined hormonal contraception should be conducted to rule out contraindications or potential drug interactions.
How to be reasonably certain that a woman is not pregnant

- A medical history can accurately determine when a woman is not pregnant (see criteria in Appendix 1).
- Routine pregnancy tests for every woman are not necessary and should be based on clinical judgement, keeping in mind that test accuracy is dependent on several factors including recent sexual intercourse or early pregnancy.

When is a woman most likely to get pregnant?

During an average 28 day cycle, ovulation generally occurs during days 9-20.
- The likelihood of ovulation is low on days 1-7 of menstrual cycle.
- Return of ovulation:
  - Post spontaneous or induced abortion: 2-3 weeks but as early as 8-13 days
  - Postpartum, non-lactating women: mean 45-94 days but as early as 25 days
- Among women who are within 6 months postpartum, are fully or nearly fully breastfeeding (≥85%) and are amenorrheic, the risk for pregnancy is <2%.
- Return of fertility post combined contraceptive discontinuation:
  - Following continuous use of levonorgestrel (LN) 90 mcg and ethinyl estradiol (EE) 20 mcg, Barnhart et al\textsuperscript{57} report a pregnancy rate of 57% at 3 months, 81% at 12 months, and 86% (18 of 21) (95% confidence interval 64% to 97%) at 13 months after discontinuation of treatment.
  - A prospective European study\textsuperscript{4} reports 21.1% (95% CI 19.4-23.0%) of past oral-contraceptive users pregnant one cycle after oral-contraceptive cessation and 79.4% (95% CI 77.6-81.1%) at 1 year.
    - No major influence of progestin type, EE dose, duration of oral-contraceptive use, and parity on the rate of pregnancy after oral-contraceptive cessation.
    - Up to age 35 years, age had only a minor influence on the rate of pregnancy. Rates of pregnancy were reduced in women older than 35 years and in current smokers.
- Return of fertility can be delayed for up to 1 year after discontinuation of progestogen-only injectable contraception.
  - The Depo-Provera\textsuperscript{®} (DMPA) product monograph cites a large study of return of fertility which showed that women conceived 9 months on average after the last injection, or 5.5 months after discontinuing (discontinuance is assumed to be 15 weeks after the last injection).\textsuperscript{5}
Resources and Links

The information contained in this document has been primarily derived from the

- Centers for Disease Control and Prevention (CDC), U.S. Selected Practice Recommendations for Contraceptive Use.¹³
  http://www.cdc.gov/mmwr/pdf/rr/rr6205.pdf
  • Endorsed by the American Congress of Obstetricians and Gynecologists (ACOG)¹⁶
    http://www.acog.org/Womens-Health/Birth-Control-Contraception

- World Health Organization (WHO)⁷
  http://www.who.int/reproductivehealth/publications/family_planning/en/

- Guidelines from the Society of Obstetricians and Gynecologists of Canada (SOGC)⁸
  http://sogc.org/clinical-practice-guidelines/

- Faculty of Sexual and Reproductive Healthcare⁹
  • Drug interactions¹⁰
    http://www.fsrh.org/pdfs/CEUguidancedruginteractionshormonal.pdf
  • Women over 40 years¹¹

- Health Canada warnings
  • Drospirenone
  • Cyproterone

- http://www.sexualityandu.ca/ - many links to resources e.g.,
  • Contraceptive methods
    http://www.sexualityandu.ca/health-care-professionals/contraceptive-methods
  • Sexual Behaviors in teenagers
  • Emergency Contraception
    http://www.sexualityandu.ca/health-care-professionals/contraceptive-methods/emergency-contraception
  • Birth Control FAQs
    http://www.sexualityandu.ca/faqs/birth-control

- CDC I Phone app
  https://itunes.apple.com/ca/app/contraception/id595752188?mt=8

- Canadian Medical Association members
  o Readers interested in the topic of Abnormal Uterine Bleeding are referred to a detailed review of this topic in Essential Evidence Plus.

- Systematic reviews (e.g., Cochrane Reviews), clinical trials, and epidemiological data.
NOTE: Product monograph and patient information developed by manufacturers may differ slightly from information in this document.

We have addressed five clinical questions:

1. What are the clinical considerations for healthy women requesting contraception?
2. What is the comparative effectiveness of contraception methods?
3. What are the special circumstances or risks when choosing a contraception method?
4. What are the regimens to use when emergency contraception is needed?
5. Is there evidence for other non-contraceptive benefits or harms of combined hormonal contraceptives?
Question 1: What are the clinical considerations for healthy women requesting contraception?

Prescribing Pearls for all Contraceptives

- Medical and drug history should be conducted to determine medical eligibility for chosen contraceptive method. See medical eligibility in Appendix 3.
- Clinically exclude pregnancy (see Appendix 1).
- Enhanced counseling on appropriate use and adverse effects may improve compliance and reduce method discontinuation. The discontinuation rate in trials is approximately 45%.
- Among couples attempting to avoid pregnancy the percentage who continue the method of contraception at 1 year is approximately 67% for combined hormonal contraceptives (CHCs) and progestin only pills (POPs), 56% for progestin injection and up to 80% for IUD users.\(^3\)\(^{12}\)
- Give the chosen contraceptive a reasonable trial; often side effects will be overcome within approximately 3 to 6 months.
- Consistent and correct use of male latex condoms are required to reduce the risk of STDs.
- The CDC suggests weight and body mass index (BMI) measurements are not needed to determine medical eligibility for any methods of contraception because all methods can be used or generally can be used among obese women. Measuring weight and calculating BMI at baseline might be helpful for monitoring weight changes perceived to be associated with their contraceptive method.
- Emergency contraception can be considered in addition to any method of contraception in situations where it is considered appropriate.
- Removing unnecessary barriers can help patients access and be successful with their contraception.\(^3\)
  - Medical barriers to initiating and continuing contraceptive methods include:
    - Unnecessary screening examinations and tests before starting the method (e.g., a pelvic examination before initiation of combined oral contraceptives COCs);
    - Inability to start contraceptive on day of practitioner visit (e.g., waiting for unnecessary test results or waiting until the woman’s next menstrual period); and
    - Inability to obtain contraceptive supplies (e.g., restrictions on number of pill packs dispensed at one time).
- Benefits of starting contraception may outweigh risks (except insertion of an IUD) when it is reasonably certain that the woman is not pregnant; contraception can be started and a pregnancy test done in 2-4 weeks.\(^3\)
- The “quick-start” method with CHC, (first pill is started on the day of office visit, provided she is not pregnant), may also be used. A back-up method of contraception is required for the first 7 days unless the 1st day of last menstrual period was ≤ 5 days ago. This method may increase adherence, with no associated increase in breakthrough bleeding or other side effects.\(^13\)
- There is no increased risk for adverse outcomes to infants exposed to combined oral contraceptives or depot medroxyprogesterone acetate in utero.\(^3\)
There are clinical considerations for prescribing contraceptives in otherwise *healthy* women, including:

- **Age**;
- **Increased weight or obesity**;
- **Acne indication**;
- **Smoking**;
- **Migraine**; and
- **Blood pressure assessment**.

**Age**

- The risk of cardiovascular disease increases with age and may also increase with combined hormonal contraceptive use. In **non-smokers** and the absence of other adverse clinical conditions, guidelines suggest that combined hormonal contraceptives can be used until menopause, aged 50-55, although evidence is lacking in this age group.³
- Combined hormonal contraceptive is **not recommended** in women > 35 years of age who are smokers.
- **Adolescents**: The recommendations in CDC guidelines apply to all healthy women including adolescents.
  - CDC considers adolescence a special population that might benefit from more frequent follow-up.
  - In general, adolescents are eligible to use any method of contraception and must have access to a variety of contraceptive choices.
  - Age alone does not constitute a medical reason for denying any method to adolescents.
  - The advantages of avoiding pregnancy in adolescents should be balanced against concerns regarding the use of certain contraceptive methods in adolescents (e.g. the potential decrease in bone mineral density with the use of progestogen-only injection by those below 18 years).³

**Increased Weight or Obesity**

- It has been suggested that the effectiveness of hormonal contraceptives may be related to metabolic changes in obesity, greater body mass or body fat.
  - A 2013 Cochrane Review by Lopez et al. examined whether these factors had any impact on unplanned pregnancies among women who are overweight or obese versus women of lower weight or body mass index (BMI).¹⁴
    - In the 13 studies reviewed (N=49,712), there was generally no evidence that BMI affected combined hormonal contraceptives efficacy.
    - One of five studies categorizing outcomes by BMI reported a higher pregnancy risk for overweight or obese women.
      - Increased risk of pregnancy in women with BMI ≥ 25 versus < 25 taking norethindrone acetate 1.0 mg plus EE 20 μg (RR 2.49; 95% CI 1.01 to 6.13). However, if the BMI cutoff of ≥ 27.3 was used then risks were similar between groups.
• The other four studies that did not find a significant difference by BMI studied an extended-regimen for a combined oral contraceptive, an injectable and a transdermal skin patch.
• The authors caution there was limited evidence for any individual contraceptive method and the overall quality of evidence was low.
  - IUDs can be used in women who are obese (> 30 kg/m²).³
  - The CDC recommends that screening for obesity (weight/BMI) is not necessary for the safe initiation of combined oral contraception, progestin-only contraception or IUD insertion, as all can generally be used by obese women.³

Acne Indication
  - Several combined oral contraceptive pills with EE and LNG are indicated for both contraception and treatment of acne vulgaris: e.g., Alesse®, Alysena®, Aviane®, ESME, Lutera®.⁵
  - Other products e.g., Diane 35® and Cyestra 35® contain the antiandrogen cyproterone; as well as, ethinyl estradiol (EE) and are indicated only for treatment of acne vulgaris.
    - These agents should not be prescribed for the purpose of contraception alone; however, when taken as recommended will provide reliable contraception.⁵
    - Some but not all reports suggest a higher risk of VTE with products containing cyproterone. Please refer to section on VTE pg. 31.
  - A Cochrane Review¹⁵ including 31 trials with 12,579 participants taking combined oral contraceptives concluded:
    - Of nine placebo-controlled trials with data for analysis, all showed COCs reduced acne lesion counts, severity grades and self-assessed acne compared to placebo.
    - Several different progestins were examined in the trials, including those available in products in Canada: levonorgestrel, norethindrone acetate, norgestimate, drospirenone, dienogest and cyproterone.
    - Few important and consistent differences were found between COC types in their effectiveness for treating acne, although products containing cyproterone seem to improve acne better than those containing levonorgestrel. This conclusion is based on limited evidence.

Smoking
  - Medical eligibility considerations for women < 35 who smoke suggest advantages of CHC generally outweigh proven or theoretical risks; however alternative contraceptives that do not contain estrogen have no restrictions on use.
  - CHC is not recommended in women over 35 years of age who smoke (see section on VTE/CVD and Medical Eligibility Charts¹⁸ Appendix 3).
  - Smokers with no other medical conditions can use progestin only contraceptives (oral, injectable or IUD) or the copper IUD without restrictions.³
Migraine

- Guidelines have developed recommendations for contraception in patients with co-existing migraines, with and without visual aura. Migraine with visual aura is a risk factor for stroke and concomitant use of COCs further increases this risk (see section on stroke, pg. 36).²,¹⁶,¹⁷
- The majority of guidelines state that contraceptive estrogen/progestin combinations should not be used in women of any age who experience migraines with aura, as there is an unacceptable increased risk for stroke. While the absolute risk may be small, the effects can be devastating, especially considering that alternative methods of contraception are available (see Appendix 3).³,¹⁶,¹⁷,¹⁸
  - Increased frequency of migraines with aura and higher estrogen doses have been associated with increased risk of stroke.¹⁹
- In women with migraine without aura who are age > 35 years, combined estrogen/progestin contraception is not usually recommended unless other more appropriate methods are not available or not acceptable.
- In women with migraine without aura, < 35 years of age, combined estrogen/progestin contraception is considered to have advantages that outweigh theoretical or proven risks.
- Women with non-migranous headaches can use all forms of contraception without restriction.³

NOTE: According to the Medical Eligibility Charts¹⁸ (Appendix 3), copper IUDs have no restrictions on use in patients with migraine with aura while for progestin only contraceptives (oral or IUD), it is considered that the advantages generally outweigh theoretical or proven risks.
Question 2: What is the comparative effectiveness of contraceptive methods?

- The Pearl Index (number of pregnancies per 100 woman years) is a common measure used to estimate contraceptive effectiveness.
  - It has been reported that Pearl Indices for newer contraceptives have been increasing. Trussell and Portman (2013) examined the literature and concluded that more frequent pregnancy testing with more sensitive tests and less adherent study populations were the most likely reasons for this phenomenon. It is a consideration when assessing new products.
  - The reported failure rate of oral contraceptives is generally the same, approximately 9% with usual use and 0.3% with perfect use.
  - Nine out of 100 women become pregnant with usual use of COCs and POPs in the first year.
  - Rates apply to various formulations of monophasic (strength of estrogen or type of progestin used), or triphasic combined oral contraceptives; patches or progestin only oral contraceptives or vaginal ring.
    - A new COC containing the lowest estrogen dose (LoLo™ 1 mg NA plus EE 10 mcg) report the pregnancy rate (Pearl Index) in women 18-35 years of age as 2.92 pregnancies per 100 women-years of use from clinical trial data.
  - There are similar efficacy rates irrespective of packaging (21 day, 28 day, 3 months).
  - Evidence suggests the more pill packs given up to 13 cycles, the higher the continuation rates, fewer pregnancy tests and lower costs.

- IUDs offer enhanced efficacy rates with failure reported as 0.2%, as compliance is not a factor.

- Consistent and correct use of male latex condoms are required to reduce the risk of STDs, including HIV.

- The diagram below describes effectiveness with “typical use.”
Combined Hormonal Contraception (CHC)

- Combined hormonal contraceptives contain estrogen and progestin and include combined oral contraceptives (COCs), transdermal patches and a vaginal contraceptive ring.

- A medical and drug history to assess medical eligibility for CHC should be conducted to rule out contraindications and potential drug interactions.

- **Contraindications to all formats of combined hormonal contraceptives** – Please refer to Medical Eligibility Charts for detailed contraindications and cautions.18

  - Current breast cancer
  - Migraines with aura (any age)
  - Hypertension - should generally not use. Definitely should not use if severe. i.e., systolic ≥ 160; diastolic ≥ 100 mmHg
  - Ischemic heart disease/vascular disease/past or current DVT/thrombogenic mutations
  - Certain liver diseases
  - Smokers ≥ 35 years old and ≥ 15 cigs/day
  - Complicated diabetes
  - 3-4 weeks postpartum
  - Up to 6 weeks post cesarean section
Among **healthy women, few examinations or tests are needed** before initiation of combined hormonal contraceptives.

Examination and tests considered **essential and mandatory** in all circumstances for safe and effective use of CHC³:

- **Blood pressure**
  - Systolic BP 140-159 or diastolic BP 90-99: the theoretical or proven risks of CHC generally outweigh advantages
  - Systolic BP ≥ 160 or diastolic BP ≥ 100 or presence of vascular disease presents an **unacceptable health risk for CHC use**

- These tests are rated as "**Class C**" by the CDC (i.e., do not contribute substantially to safe and effective use of the contraceptive method in healthy women):
  - Clinical breast examination;
  - Bimanual examination and cervical inspection;
  - Glucose;
  - Lipids;
  - Liver enzymes;
  - Hemoglobin;
  - Thrombogenic mutations;
  - Cervical cytology (Papanicolaou smear);
  - STD screening with laboratory tests; and
  - HIV screening with laboratory tests.

- Weight and BMI are **not necessary** to determine medical eligibility. However, monitoring changes may be helpful to counsel women who might be concerned about weight change perceived to be associated with their contraceptive method.³

A 2014 Cochrane Review (4 studies)²² found no evidence for a causal association in weight changes between users and non-users of combination oral contraceptives or skin patches. Comparisons between different products also showed no substantial differences in weight. Despite no large effect on weight, due to limitations with available evidence, the review concluded there is **insufficient evidence** to determine the effect of combination contraceptives on **weight**.

- As a general rule, unless CHC is initiated within the first 5 days since the start of menstrual bleeding, additional contraception or abstinence from sexual intercourse is required for **7 continuous days** of combined contraceptive use. This may not apply to postpartum women – please see Table 2.
  - If < 6 months postpartum, amenorrheic, and fully or nearly fully breastfeeding (exclusively breastfeeding or the vast majority [≥85%] of feeds are breastfeeds), no additional contraceptive protection is needed (Lactational Amenorrheic Method). Otherwise, if ≥ 21 days postpartum and menstrual cycles have not returned, abstain from sexual intercourse or use additional contraceptive protection for the **next 7 days**.³
Continuous or Extended Use Oral Contraceptive

- **Continuous use** is defined as uninterrupted use of hormonal contraception without a hormone-free interval. **Extended use** is defined as a planned hormone-free interval after at least two contiguous cycles.³
- Any product with < 50 mcg of ethinyl estradiol can be used, including monophasic or multiphasic oral tablets, transdermal patches or vaginal ring.⁸,²³
  - Products packaged especially for extended or continuous use include:
    - Seasonale® (84 day pack)
    - Seasonique® (91 day pack)
- A Cochrane systematic review (12 studies) reported **similar pregnancy rates and safety profiles** for extended or continuous regimens (> 28 days) compared with 28-day regimens.
  - No difference in compliance found in trials reporting this outcome.
  - Similar rates of satisfaction and discontinuation were found in each group although the extended or continuous group reported fewer headaches, genital irritation, tiredness, bloating, and menstrual pain.²¹
- Unscheduled spotting or bleeding is common during first 3-6 months. This is generally not harmful and decreases with continued COC use.
  - If clinically indicated, investigate for underlying gynecological problems (polyps, fibroids), inconsistent use, medication interactions, cigarette smoking, STD, pregnancy and treat as appropriate.
  - If no problems identified and with patient counseling:
    - Consider a hormone free interval (stopping COC) for 3-4 consecutive days (not recommended during first 21 days of continuous or extended method, or more often than once per month as effectiveness of method might be reduced); or
    - Consider offering an alternative contraceptive method.³

Multiphasic Oral Contraceptives

- The rationale behind the development of multiphasic approaches was to improve the unsatisfactory bleeding patterns observed with monophasic preparations and attempt to mimic natural cycles.
- Van Vleit and colleagues performed Cochrane Reviews investigating differences between these approaches.²⁴,²⁵,²⁶
  - The reviews generally conclude there is **insufficient evidence** to make comparisons between multiphasic products and that **monophasic pills should be the first choice** for women starting oral contraceptive use.
    - High quality comparative data on which to base conclusions are limited.
Progestin Only Pill (POP, Minipill)

- The oral progestin only product available in Canada is norethindrone 0.35 mg (Micronor®).
- Progestin only contraception can be used by women of all ages.³
- No tests are considered essential in healthy women prior to starting progestin only contraceptives, although baseline weight and BMI may be useful for monitoring. Women with known medical problems may require additional tests to determine appropriateness.
- Women with hypertension, diabetes, hyperlipidemia, anemia, thrombogenic mutations (e.g., Factor V Leiden disease, anticardiolipin antibody), cervical intraepithelial neoplasia, cervical cancer, STDs or HIV can use, or generally can use, POPs.³
- There are few conditions where progestin only contraception is contraindicated or generally not recommended. They are not recommended in women with certain liver diseases and current breast cancer – please refer to Medical Eligibility Charts in Appendix 3.
- The pregnancy rate with POP use is the same as with combined oral contraceptives: 9 out of 100 women in the first year of typical use.
  - While most resources suggest similar pregnancy rates with progestin only and combined oral contraceptive pills, Trussel suggests that the progestin-only pill is likely less effective than the combined pill during typical use, since it is probably less forgiving of nonadherence to the dosing schedule. Whether the progestin-only pill is also less effective during perfect use is unknown.¹²
- POPs are taken daily without a hormone free interval.
- Counsel women of the importance of taking POP at the same time each day.
  - Women who frequently miss POPs should consider an alternative contraceptive method that is less dependent on the user to be effective (e.g., IUD, or injectable).
  - A dose is considered missed if it is > 3 hours since it should have been taken.
- As a general rule, unless POP is initiated within the first 5 days since the start of menstrual bleeding, additional contraception or abstinence from sexual intercourse is required for 2 continuous days of POP use. This may not apply to postpartum women – see Table 2.
  - If < 6 months postpartum, amenorrheic, and fully or nearly fully breastfeeding (exclusively breastfeeding or the vast majority [≥85%] of feeds are breastfeeds) no additional contraceptive protection is needed.
  - Otherwise, if ≥ 21 days postpartum and menstrual cycles have not returned, abstain from sexual intercourse or use additional contraceptive protection for the next 2 days.³,⁵
- Menstrual irregularity is the most frequently reported side effect of the progestin only pill.
  - Frequent and irregular bleeding is common, while long duration of bleeding episodes and amenorrhea are less likely.
Progestin Only Injectable

- The progestin only injection available in Canada is medroxyprogesterone acetate (Depo-Provera®, DMPA).
- DMPA can be initiated at any time it is reasonably certain a woman is not pregnant.
  - If started within the first 7 days since menstrual bleeding started, no additional contraceptive protection is needed.
  - If started > 7 days since menstrual bleeding started, or when amenorrheic, or switching from another method, abstain from sexual intercourse or use additional contraceptive protection for the next 7 days.
  - The DMPA injection has some circumstances where it is considered a less appropriate choice or not recommended. Please see Medical Eligibility Charts in Appendix 3.
- Pregnancy rate with first year of use of DMPA injection: approximately 6 out of 100 women in first year of typical use.3
- The use of depot medroxyprogesterone injection has been associated with weight gain of approximately 5 kg over 36 months compared with no weight gain in users of oral contraceptives.5,27
  - Studies report 2% of women discontinue DMPA due to weight gain and 20-40% lose weight.

Repeat injections

- The repeat DMPA injection can be given up to 2 weeks late (15 weeks from the last injection) without requiring additional contraceptive protection.
- If > 2 weeks late (i.e., > 15 weeks from the last injection), the injection can be given if it is reasonably certain that the woman is not pregnant, and abstains from sexual intercourse or uses additional contraceptive protection for the next 7 days.3

Intrauterine Devices (IUD)

IUDs are a form of long acting reversible contraception. With typical IUD use, less than 1 out of 100 women become pregnant in the first year. An important consideration prior to IUD insertion is being reasonably certain that the woman is not pregnant. (See Appendix 1)

- Bimanual examination and cervical inspection are essential and mandatory for safe and effective use of IUDs.3
- Products include the copper IUD (CU IUD, several products) and levonorgestrel releasing IUD (LNG-IUD – e.g., Mirena®, Jaydess®).
- A discussion of various copper IUD products is beyond the scope of this material. However, the following summarizes differences between the LNG-IUDs.
  - Jaydess® has been studied in women > 18 years old.
Mirena® product information suggests it is not the contraceptive method of first choice for young, nulligravid women although CDC and SOGC guidelines suggest IUDs can be used by all ages, including adolescents, parous and nulliparous women.

Jaydess® and Mirena® differ
- In the amount of levonorgestrel they contain (13.5 mg Jaydess® vs 52 mg Mirena®), relating to their duration of use (3 years Jaydess® and 5 years Mirena®).
- In their dimensions (Jaydess®: 28x20 mm vs. Mirena®: 32x32 mm).

The incidence of pelvic inflammatory disease (PID) or removal of IUD as a result of PID does not differ between those using copper or levonorgestrel IUDs, combined oral contraceptives, or progestin-only injections.³

The rate of PID is generally low but significantly higher in the first 20 days after insertion of IUD.

Cu IUD: Bleeding (unscheduled spotting, light bleeding or heavy or prolonged bleeding), is common during the first 3–6 months of Cu-IUD use, is generally not harmful, and decreases with continued use.

If there is no underlying gynecological problem found, consider nonsteroidal anti-inflammatory drugs (NSAIDs) for short-term treatment (5–7 days). Evidence for specific regimens for bleeding irregularities is lacking.
- If bleeding persists and is unacceptable to the woman, consider an alternative contraceptive method.³

LNG-IUD: Unscheduled spotting or light bleeding is expected during the first 3–6 months of use, is generally not harmful, and decreases with continued LNG-IUD use and many women experience only light menstrual bleeding or amenorrhea.

Approximately 50% of LNG-IUD users experience amenorrhea or oligomenorrhea by 2 years of use. Heavy or prolonged bleeding, either unscheduled or menstrual, is uncommon during LNG-IUD use.³

LNG IUD (Mirena and Jaydess) monographs suggest the risk of uterine perforation is higher in the postpartum period and during lactation.⁵

Additional Protection Following IUD Insertion³
- LNG IUD:
  - If inserted within the first 7 days since menstrual bleeding started, no additional contraceptive protection is needed.
  - If inserted > 7 days since menstrual bleeding started, or amenorrheic (not postpartum), abstain from sexual intercourse or use additional contraceptive protection for the next 7 days.

Copper IUD: No additional contraceptive protection is needed. DO NOT INSERT IUD if not reasonably certain that the woman is not pregnant. Provide another contraceptive method until reasonably certain the woman is not pregnant, and then the Cu-IUD can be inserted.
Tests Prior to IUD Insertion

- **Essential and mandatory** test in all circumstances for safe and effective use of IUDs:
  - Bimanual examination and cervical inspection.

- According to statements from the SOGC 2014, routine use of prophylactic antibiotics at the time of IUD insertion is not recommended. However, it may be used in certain high risk situations.
  - Prophylaxis with one dose of azithromycin 1 g or doxycycline 200 mg may be prescribed.

- **Sexually transmitted diseases**: Most women do not require additional STD screening at the time of IUD insertion if they have already been screened according to CDC’s STD Treatment Guidelines (available at http://www.cdc.gov/std/treatment). If a woman has not been screened according to guidelines, screening can be performed at the time of IUD insertion, and insertion should not be delayed.

- **Women with purulent cervicitis or current chlamydial infection or gonorrhea should not undergo IUD insertion**. Women who have a very high individual likelihood of STD exposure (e.g., those with a currently infected partner) generally should not undergo IUD insertion. For these women, IUD insertion should be delayed until appropriate testing and treatment occur.

**Table 1: When to start using specific contraceptive methods**

<table>
<thead>
<tr>
<th>Contraceptive method</th>
<th>When to start</th>
<th>Additional contraception (i.e. back-up) needed</th>
<th>Examinations or tests needed before initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper-containing IUD</td>
<td>Anytime</td>
<td>Not needed</td>
<td>Bimanual examination and cervical inspection</td>
</tr>
<tr>
<td>(Need negative pregnancy test)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel-releasing IUD</td>
<td>Anytime</td>
<td>If &gt; 7 days after menses started, use back-up method or abstain for 7 days</td>
<td>Bimanual examination and cervical inspection</td>
</tr>
<tr>
<td>(Need negative pregnancy test)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injectable</td>
<td>Anytime*</td>
<td>If &gt; 7 days after menses started, use back-up method or abstain for 7 days</td>
<td>None</td>
</tr>
<tr>
<td>Combined hormonal contraceptive</td>
<td>Anytime*</td>
<td>If &gt; 5 days after menses started, use back-up method or abstain for 7 days</td>
<td>Blood pressure measurement</td>
</tr>
<tr>
<td>Progestin-only Pill</td>
<td>Anytime*</td>
<td>If &gt; 5 days after menses started, use back-up method or abstain for 2 days</td>
<td>None</td>
</tr>
</tbody>
</table>

IUD= intrauterine device

*Anytime means anytime you are reasonably certain that the woman is not pregnant (See Appendix 1)

Adapted from http://www.cdc.gov/mmwr/pdf/rr/rr6205.pdf
FACTORS AFFECTING EFFICACY OF ORAL CONTRACEPTIVE METHODS

- Women should be counseled on the factors affecting efficacy and the follow-up actions required.
- Factors affecting efficacy include non-compliance, vomiting or diarrhea and clinically relevant drug interactions.

Non-Compliance

- Non-compliance – late (< 24 hours late) or missed pills (> 24 hours for COCs and > 3 hours for POPs since the time the pill should have been taken)
  - Missing pills or starting the pack late may make the contraceptive less effective. The chance of pregnancy after missing pills depends on when the pills were missed and how many were missed.\(^{29}\)
  - Please consult individual product monographs as recommended actions vary.
  - Extending the hormone free interval is considered a particularly risky time to miss CHCs. Seven days of continuous CHC use is necessary to reliably prevent ovulation.\(^3\)
  - Emergency contraception can be considered.

Vomiting or Diarrhea

- Vomiting or diarrhea for any reason has to be treated like a late or missed dose.
  - Please consult individual product monographs as recommended actions vary.
  - Emergency contraception can be considered.

Clinically Relevant Drug Interactions

- Prescribers are advised to consider potential drug interactions when adding medications to patients using contraceptive methods and check with current, reliable resources to determine clinical relevance.
- Women using hormonal contraception should be asked about concurrent drug use including over the counter medications, herbal medications (St. John’s Wort), oral retinoids, etc. and counseled to check with a health professional before starting any new drugs.
- **Antibiotics**: Controversy has existed on whether antibiotics such as amoxicillin or penicillin affect the efficacy of oral contraceptives. Available scientific and pharmacokinetic data do not support that antibiotics (with the exception of rifampin) lower the contraceptive efficacy of oral contraceptives and additional protection is not needed with short durations of use.\(^10\)
  - Of note: If antibiotics (and/or the illness) cause vomiting or diarrhea or pills are missed then the usual additional precautions should be observed and women counseled about the importance of correct contraceptive practice during periods of illness. Other drugs that induce diarrhea or cause vomiting can also decrease effectiveness of oral contraceptives.
In addition to drug interactions, the clinical effect of some drugs or conditions may also be affected by contraceptives; for example, there is potential for an increase in thyroid hormone requirement\textsuperscript{10}; drospirenone has antimineralocorticoid activity, and a potential risk for hyperkalemia comparable to a 25 mg dose of spironolactone.\textsuperscript{5}

Robust evidence for drug interactions with oral contraceptives is lacking. Most data is from case reports or observational data.

Enzyme-inducing drugs have well established drug interactions.

- From the perspective of decreasing birth control efficacy, drugs with enzyme inducing properties e.g., anti-epileptics, anti-retrovirals (protease inhibitors) and rifampin decrease the effectiveness of contraceptives, and alternative methods of contraception that are not affected by enzyme inducing drugs \textbf{should be chosen} such as the progestogen-only injection, Cu-IU or the levonorgestrel containing IUDs.
- Enzyme induction generally returns to normal within 28 days after stopping the drug.
- Women on enzyme inducing drugs or within 28 days of stopping them who require \textbf{emergency contraception} should be advised of interactions. A Cu-IUD may be an appropriate alternative.\textsuperscript{10}

\textbf{Managing Adverse Effects of Hormonal Contraceptives}\textsuperscript{30}

- There is insufficient evidence to suggest one method is superior to another in terms of adverse effects.
  - \textbf{Counselling} patients about common adverse effects helps to establish realistic expectations.
  - \textbf{Reassurance} that symptoms will likely resolve within 3 to 6 months is often the only treatment required.

- Breakthrough bleeding is common in the first months of COC use and patients should be reassured that this will likely resolve.
  - Increasing the estrogen dose above 20 mcg or changing the type of progestin has not been shown to change bleeding rates.

- Switching COCs is not effective in treating headaches and there are no significant differences among various COCs in terms of breast tenderness, mood changes and nausea.
Question 3: What are the special circumstances or risks when choosing a contraception method?

There are special circumstances or risks to consider when choosing a contraception method, including:

- Postpartum and breastfeeding considerations;
- Venous thromboembolic events (VTEs);
- Risk of stroke;
- Bone mineral density;
- Weight gain; and
- Perimenopausal considerations.

Postpartum and Breastfeeding Considerations

- Postpartum
  - If < 21 days postpartum there is theoretical concern regarding the association between combined hormonal contraceptive use and the risk of thrombosis in the mother. Blood coagulation and fibrinolysis are essentially normalized by three weeks postpartum.³
  - For women who are medically eligible, delay starting CHCs until 4 weeks if breastfeeding and 6 weeks if the woman has other risk factors for VTE.³¹
Table 2: Postpartum contraception initiation and breastfeeding considerations

<table>
<thead>
<tr>
<th>Type</th>
<th>Timing</th>
<th>Need for back-up contraception</th>
<th>Prescribing Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type of combined hormonal contraceptive</td>
<td>Postpartum (Breastfeeding)</td>
<td>&lt;6 months postpartum, amenorrheic, and fully or nearly fully breastfeeding (exclusively breastfeeding or the vast majority [≥85%] of feeds are breastfeeds) no additional contraceptive protection is needed.</td>
<td>Can be initiated when medically eligible for the method and it is reasonably certain the woman is not pregnant. Postpartum women should not use combined hormonal contraceptives during first 3 weeks after delivery as this represents an unacceptable health risk for VTE. Do not generally use in 4th week postpartum due to concerns with potential effects on breastfeeding performance. Postpartum with other risk factors (e.g. age &gt; 35, smoker, post C-section, immobility) for VTE should generally delay starting CHC until 42 days after delivery.</td>
</tr>
<tr>
<td></td>
<td>Postpartum (Not breastfeeding)</td>
<td>Otherwise, if ≥21 days postpartum and menstrual cycles have not returned, abstain from sexual intercourse or use additional contraceptive protection for the next 7 days. If menstrual cycles returned and &gt;5 days since menstrual bleeding started, abstain from sexual intercourse or use additional contraceptive protection for the next 7 days.</td>
<td></td>
</tr>
<tr>
<td>Oral, patch, ring</td>
<td>Breastfeeding: If &lt;6 months postpartum, amenorrheic, and fully or nearly fully breastfeeding (exclusively breastfeeding or the vast majority [≥85%] of feeds are breastfeeds), no additional contraceptive protection is needed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postpartum (Breastfeeding or not breastfeeding)</td>
<td>Otherwise, if ≥21 days postpartum and no return of menstrual cycles, abstain from sexual intercourse or use additional contraceptive protection for the next 2 days. If menstrual cycles have returned and &gt;5 days since menstrual bleeding started, abstain from sexual intercourse or use additional contraceptive protection for the next 2 days.</td>
<td></td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism

➢ Breasftfeeding considerations
  o A recent Cochrane Review\textsuperscript{32} investigated the effects of hormonal contraceptives on lactation and infant growth.
    ● Most trials did not show or report significant differences between study arms in breastfeeding duration, breast milk composition, or infant growth.
    ● Breastfeeding continuation was studied in eight trials. One older study reported a negative effect of a combined oral contraceptive (COC) on lactation duration but did not quantify results. An early trial of a levonorgestrel-releasing intrauterine device (LNG-IUDs) showed a lower percentage of the LNG-IUD group breastfeeding at 75 days but no significant difference at one year. The other five trials indicated no significant differences between the study arms.
- **Infant growth** was assessed in seven trials. One showed greater infant weight gain for the etonogestrel implant group than for the no-method group during the first six weeks. The implant group had less weight gain from 6 to 12 weeks when compared to those given depot medroxyprogesterone acetate (DMPA). The other six studied POPs only, COCs versus POPs, or the LNG-IUD, and indicated no significant differences between groups. Trial reports did not present the amount of supplemental feeding provided to the infants.

- For **breast milk volume**, two older studies indicated lower volume for the COC group versus the placebo group yet four trials did not report any significant difference between the study groups in milk volume or composition with two progestin only pills, a combined oral contraceptive or a progestin implant.

**Venous Thromboembolic Events (VTE)**

**Risk of VTE in women**

- The risk of VTE in estrogen-containing COC users is very low and for the majority of women the benefits outweigh the risks.

- Reports of differences in VTE risk between types of combined hormonal contraceptives are **contradictory** with some finding a statistically significant increased risk, while others do not. This is generally reflective of the risk of bias in the studies included in the analyses.

- The classification of progestins as second, third or fourth generation is not science–based and not standardized and may differ in studies and guidelines. For example, norgestimate has been classified as both a second and third generation progestin.

**Table 3: VTE Rates according to risk factor**

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>RATE (Cases VTE per 10,000 women per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline risk during reproductive years, women using progestin only pills or progestin IUD</td>
<td>4-5</td>
</tr>
<tr>
<td>Combined hormonal contraceptive</td>
<td>8-9</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Up to 29</td>
</tr>
<tr>
<td>Peripartum period</td>
<td>As high as 300-400</td>
</tr>
</tbody>
</table>

- According to Statistics Canada, there are approximately 200,000 women in Nova Scotia between the ages of 15 and 50. The baseline rate of VTE is approximately 100 per 200,000 women per year which would increase to 200 per year if they all took CHCs.

- Contraceptive use reduces rates of unplanned pregnancies and actually decreases the overall rate of VTE in the population in comparison to populations without access to effective contraception.
  
  - The risk of VTE in pregnancy and the postpartum period is much higher than with CHC use.
- When identified and treated appropriately with anticoagulation, most cases of VTE resolve.
  - However, if a pulmonary embolism results, the fatality rate is 1%.
  - The VTE death rate due to oral contraceptive use is <1/100,000 women per year which is similar to the risk of death from other uncommon causes (e.g. falls, drowning, poisoning, domestic violence) and much lower than the risk associated with pregnancy (8/100,000).

- Health-care providers should:
  - Assess risk factors for VTE as one component of identifying the optimal choice of contraception for a given woman.
    - Risk factors include advancing age (>35 years), cigarette smoking, immobility, obesity and pregnancy and the postpartum period.\(^{35}\)
    - For example, cigarette smoking has been associated with a twofold increased risk of VTE in CHC users compared to non-smokers using CHC. This risk is almost tripled in heavy smokers.\(^{36}\)
  - Understand that the risk of VTE in COC users is highest in the first months of use, falling towards baseline thereafter. Pill breaks should be discouraged as there is no evidence of benefit and breaks of one or more treatment cycles may reintroduce the elevated risk that occurs when COCs are re-initiated.
  - Counsel women about the risk of VTE with any estrogen-containing hormonal contraceptive and advise about signs and symptoms and what to do if these occur.\(^{33}\)

- A 2014 Cochrane Network Meta-analysis\(^{37}\) of cohort and case control studies reported a dose related increased risk of VTE with estrogen and certain progestogens:
  - Incidence of VTE in non-users of COCs, derived from two cohorts, was between 0.19 and 0.37 per 1000 person years which is comparable to previous reports of 0.16 per 1000 person years.
  - Overall, COCs increased the risk of VTE compared with non-use (RR 3.5, 95% CI 2.9 to 4.3).
  - The relative risk of venous thrombosis for COCs with 30-50 mcg EE and desogestrel, cyproterone acetate or drospirenone were similar and about 50-80% higher than levonorgestrel containing CHCs.
  - Compared with non-users, the risk of VTE with preparations containing between 30 to 35 mcg EE increased with different generations of progestogens:
    - 1\(^{st}\) generation (norethindrone) RR 3.2 (95% CI 2.0 to 5.1)
    - 2\(^{nd}\) generation (norgestrel and levonorgestrel) RR 2.8 (95% CI 2.0 to 4.1)
    - 3\(^{rd}\) generation (desogestrel, norgestimate) RR 3.8 (95% CI 2.7 to 5.4)
  Of note, although norgestimate was classified as a third generation progestin none of the comparisons in the network meta-analysis demonstrated a significantly increased risk vs. any other generation of progestin.
The risk of venous thrombosis in second generation progestogen users was similar to the risk in first generation users (RR 0.9, 95% CI 0.6 to 1.4).

Third generation progestogens had a slightly higher risk compared with second generation (RR 1.3, 95% CI 1.0 to 1.8).
- In absolute terms, if third generation progestogens increase risk by 4 - 5 times, then incidence rises to 0.76 – 1.85 cases of VTE per 1000 person-years.

In 2013, the SOGC prepared two position statements addressing the controversy on whether certain hormonal contraceptives have a lower risk of VTE than others, in particular drospirenone and cyproterone (CPA).  

These statements summarized evidence from both prospectively designed and retrospective database studies and highlighted the importance to consider the strength of evidence provided by each. The following recommendations specific to the products are presented:
- Cyproterone (e.g., Diane 35®, Cyestra®, etc.): The risk of VTE in CPA/EE users is very low and comparable to that of other combined hormonal contraceptives. For the majority of women the benefits outweigh the risks.
- Drospirenone (e.g., Yaz®, Yasmin®, etc.): Women using COCs should be advised that the highest quality evidence available at this time does not suggest a difference in VTE risk based on the type of progestin in the COC.

In 2011, the Canadian Agency for Drugs and Technologies in Health (CADTH) investigated the safety of the progestin drospirenone compared to other combined hormone contraceptive.
- The key message stated “there is no clear consensus in the literature as to the safety or relative risk of venous thromboembolism for a drospirenone/ethinyl estradiol combined oral contraceptive pill versus other forms of combined hormonal contraceptives.” The evidence reviewed included one systematic review, two randomized controlled trials, and seven non-randomized studies.
- Some studies found an increased risk with drospirenone containing OCs compared with other combined hormone contraceptives, whereas others did not.
- One systematic review on the topic could draw no formal conclusions due to methodological errors in the included studies.

The European Medicines Agency (EMA) completed a review of combined hormonal contraceptives (CHCs), particularly of the risk of VTE associated with their use.
- The review concluded that, while the benefits of OCs continue to outweigh the risks, there are differences between combined hormonal contraceptives depending on the type of progestogen which range from 5 to 12 VTEs per 10,000 women per year compared with 2 cases per 10,000 women per year who are not using CHCs.
Table 4: VTE Rates according to type of progestogen

<table>
<thead>
<tr>
<th>Type of progestogen</th>
<th>Rate (Cases VTE per 10,000 women per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not using CHC/not pregnant</td>
<td>2</td>
</tr>
<tr>
<td>Levonorgestrel/norethindrone/norgestimate</td>
<td>5-7</td>
</tr>
<tr>
<td>Drospirenone/gestodene/desogestrel</td>
<td>9-12</td>
</tr>
</tbody>
</table>

- **Non Oral Combined Contraceptives**
  - A cohort study in Denmark,\(^{40}\) found an increased risk of VTE in women using CHC transdermal patches approximately double that of oral combined hormonal contraceptives, [Rate Ratio 2.3 (95% CI 1.0 to 5.2)] and approximately 8 times that of non-users. Combined hormonal vaginal rings increased the risk to a similar extent.
    - Analysis by age demonstrated a progressive increase in risk with age.
    - Limitations of a cohort study should be acknowledged as well as the relatively low number of events that contributed to the analysis (6 confirmed cases of VTE in 6178 person years with patch and 39 per 50 334 person years for the vaginal ring).

- **Estrogen Dose**
  - The dose of estrogen (i.e. \(\geq 50\) mcg EE) in older preparations was associated with greater risk of VTE than doses less than 50 mcg.
    - Many currently available OCs contain less than 35 mcg EE. However, there is no conclusive data to suggest progressively lower risks of VTE and lower EE doses must be balanced against the potential for increased risks of breakthrough bleeding leading to nonadherence.\(^{33,35}\)
SUMMARY

- The risk for VTE is higher in women taking combined oral contraceptives than in those who do not; however the absolute risk is low and substantially less than during pregnancy or the postpartum period. It has been estimated that 2000 women would need to switch to a low risk combined oral contraceptive to prevent 1 VTE per year.\(^{41}\)

- The risk of VTE in COC users is highest in the first months of use, falling towards baseline thereafter. Pill breaks should be discouraged as the elevated risk may occur when COCs are re-initiated.

- Research demonstrates that COCs with estrogen in daily doses \(\leq 35\) mcg EE carry a lower risk of VTE than those with 50 mcg EE. There are insufficient data to suggest progressively lower risk with EE less than 35 mcg.\(^{33,35}\)

- There are conflicting data and therefore uncertainty on whether risks differ due to the type of progestin.
  - Epidemiological studies tend to report an increased risk with drospirenone and cyproterone.
    - Epidemiological studies may not control for other risk factors such as age, obesity, smoking, family history, etc.
  - Prospectively designed studies tend to report no increased risk between different progestins.

- **Cyproterone** (e.g., Diane 35®, Cyestra®, etc.) product information carries a warning that it appears to have an elevated risk of venous thromboembolic events compared to users of levonorgestrel-containing combined oral contraceptives.\(^{5}\)

- **Drospirenone** (e.g., Yaz®, Yasmin®, etc.) product information instructs prescribers to consider the benefits and risks with respect to VTE risk given the current retrospective epidemiological studies suggesting a higher risk of VTE compared to levonorgestrel-containing COCs.\(^{5}\)

- Healthcare providers should consider a woman’s current risk factors and re-assess risk over time. Patients should be counselled on the signs and symptoms of VTE when prescribed a CHC.

- Progestin only contraception (e.g., Micronor®, Mirena®, Depo-Provera®) carries no apparent increased risk of VTE or stroke.\(^{13}\)

- The **Academic Detailing Service** agrees with recommendations that, given the uncertainty, it seems reasonable to prescribe COCs containing progestins with potentially lower risk of VTE such as levonorgestrel or norethindrone as first choice. In women who are already at increased risk due to existing risk factors for VTE, prescribing a progestin only preparation is preferable.
**Risk of Stroke**

Screening for risk factors for stroke is recommended in guidelines.

According to the American Heart Association:

- Combined oral contraceptives increase the risk of stroke approximately twofold over non-users.
  - The majority of evidence is from cohort or case control studies and primarily refers to ischemic strokes.
  - Evidence for increased risk of hemorrhagic strokes is less consistent.

- **The risk of stroke is very low in the age group of women** who use contraception, but the incidence rises steeply from 3.4 per 100,000 at ages 15 to 19 years to 64.4 per 100,000 in women aged 45 to 49 years.

- Subgroups of women may be at higher risk for stroke, including women who are older, smoke cigarettes, have hypertension, diabetes, obesity, hypercholesterolemia, and prothrombotic mutations.

- The American Heart Association guidelines advocate for **blood pressure evaluation** prior to hormonal contraceptive initiation, as well as the treatment of stroke risk factors among oral contraceptive users.

- To put this into perspective, stroke rates are higher in pregnant than non-pregnant women (34 vs. 21 per 100,000), with the highest risk in the third trimester and postpartum.

**Canadian Stroke Best Practice Guidelines**

- Lifestyle and risk factor management:
  - Women taking combined oral contraceptive or hormone replacement therapy (HRT) may be at an increased risk of stroke.
  - In terms of elevated risk of stroke associated with hormonal forms of birth control, the evidence is ambiguous.
    - One large Danish cohort study including the results of over 1.6 million women between the ages of 15 and 49 years, reported that current use of ethinyl estradiol at doses of 20 to 50 μg was associated with an increased risk of thrombotic stroke (RR 1.4 to 2.2, compared with nonusers), while current use of progestin only was not.
    - The rates of thrombotic stroke increased by a factor of 20 with increasing age.
    - A large cohort study of 49,259 Swedish women aged 30-49, reported that the risk of fatal or nonfatal ischemic or hemorrhagic stroke was not significantly increased. The associations were not influenced by age at menarche nor with parity status.
  - In women who have had a stroke, estrogen-containing oral contraceptives or hormone replacement therapy should be discontinued. Management alternatives should be considered in these patients.
Migraine with aura is associated with an increased risk for ischemic and hemorrhagic stroke in women, especially in women under the age of 55 years.

- Some evidence supports a further increase in risk for women who also use OCs.
- A 2014 American Heart and American Stroke Guideline for stroke prevention in women reports the results of a population based, case control study in women aged 15-49 experiencing a stroke:
  - Migraine with visual aura increased the risk for stroke compared with controls: OR 1.5 (95% CI, 1.1–2.0);
  - Migraine with visual aura plus smoking cigarettes plus combined oral contraceptive use further increased the risk of stroke: OR 7 (95% CI, 1.3–22.8) compared with women with migraine with visual aura who did not smoke or use OCs; and
  - Women with migraine with visual aura who used OCs but did not smoke did not have an increased risk of stroke.\textsuperscript{17,44}

- It has been questioned whether currently used COCs with low estrogen dosage modify the risk of stroke. The 2013 Canadian Headache Society Guideline for Migraine Headaches references a review by MacGregor that concluded low-dose COCs are associated with a twofold increased risk of ischemic stroke compared with nonusers. The guideline suggests that, “given the availability of other contraceptive methods; it is difficult to justify exposing women with migraine with aura to these risks solely for contraception”.\textsuperscript{16,45}

- The CDC Medical Eligibility Criteria consider migraine with aura at any age an unacceptable health risk for use of combined hormonal contraception. See Appendix 3.

**Bone Mineral Density**

Hormonal contraceptive use has been associated with changes in bone mineral density but it is not clear whether there is an effect on rates of fracture later in life.

- A Cochrane Review\textsuperscript{46} investigated the evidence from RCTs on the effects of hormonal contraceptives on bone fractures in women.
  - 19 RCTs included in analysis
  - Eleven trials compared different combined oral contraceptives (COCs) or regimens of COCs; five examined an injectable versus another injectable, implant, or IUD; two studied implants, and one compared the transdermal patch versus the vaginal ring.
  - No trial had fracture as an outcome; BMD and biochemical markers of bone turnover were the surrogate outcomes used.
    - DMPA was associated with decreased bone mineral density (BMD). Bone turnover markers showed similar results.
    - The authors suggest that whether steroidal contraceptives influence fracture risk cannot be determined from existing information. Progestin-only contraceptives are considered appropriate for women who should avoid estrogen due to medical conditions.
None of the studies of combination oral contraceptives in the review were placebo controlled. There was no negative effect on BMD or bone turnover markers, and some formulations had more positive effects than others. Stronger evidence is required to determine whether CHCs have any effect on fracture risk.

- Depot medroxyprogesterone Acetate (DMPA) (Depo-Provera®) product information states:
  - DMPA has been associated with loss of bone mineral density which may not be completely reversible;
  - Loss of bone mineral density is greater with increasing duration of use;
  - This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion; and
  - It is unknown if DMPA use during adolescence or early adulthood will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.\(^5\)

- ACOG makes the following consensus based recommendation:
  - Short or long-term use of DMPA in healthy women should not be considered an indication for dual-energy X-ray absorptiometry (DXA) or other tests that assess bone mineral density.
  - In adolescents, the advantages of DMPA likely outweigh the theoretical safety concerns regarding bone mineral density and fractures. However, in the absence of long-term data in this population, consideration of long-term use should be individualized.\(^6\)

### Weight Gain

According to the product monograph for depot medroxyprogesterone acetate IM injection:\(^5\)

- The majority of studies report a mean weight gain of 5.4 lbs (2.5 kg) at the end of 1 year which may increase to 8 lbs (3.6 kg) by 2 years;
- 2% of women discontinued treatment due to excessive weight gain; and
- Some women (20-40%) lost weight during treatment.

### Perimenopausal Considerations

- The median age of menopause is 51 years but can vary from ages 40-60 years.
- The progestin only pill and IUD can be used by women until menopause.\(^18\)
- Combined oral contraceptives may have some benefits in perimenopausal women on bone mineral density and vasomotor symptoms; as well as the reduced risk in ovarian and endometrial cancers. However these benefits must be weighed against age-related increases in obesity and cardiovascular disease, such as VTE.
When can Women Stop Using Contraception?³

- Contraceptive protection is still needed for women aged > 44 years if the woman wants to avoid pregnancy.
  - The age at which a woman is no longer at risk for pregnancy is not known. Although uncommon, spontaneous pregnancies occur among women aged > 44 years.
- The median age of menopause is approximately 51 years in North America but can vary from ages 40 to 60 years.
- The median age of definitive loss of natural fertility is 41 years but can range up to age 51 years.
- No reliable laboratory tests are available to confirm definitive loss of fertility in a woman.
  - The assessment of follicle-stimulating hormone levels to determine when a woman is no longer fertile might not be accurate.
- Consider the risks of pregnancy in advanced reproductive age, as well as any risks of continuing contraception until menopause.
  - Higher risk for maternal complications at advanced reproductive age including:
    - Hemorrhage, venous thromboembolism, and death, and fetal complications, such as spontaneous abortion, stillbirth, and congenital anomalies.
  - Risks associated with continuing contraception including:
    - Acute cardiovascular events (venous thromboembolism, myocardial infarction, or stroke) or potential increased risk of breast cancer.
- Medical eligibility charts¹⁸ suggest on the basis of age alone,
  - Women aged >45 years can use POPs, implants, the LNG-IUD, or the Cu-IUD
  - Women aged >45 years generally can use combined hormonal contraceptives and DMPA
    - Women in this age group might have chronic conditions or other risk factors that might render use of hormonal contraceptive methods unsafe.
- Women using non-hormonal methods of contraception can be advised to stop contraception after 1 year of amenorrhea if aged over 50 years, 2 years if the woman is aged under 50 years.¹¹
Question 4: What are the regimens to use when emergency contraception is needed?

Emergency contraception (EC) is defined as contraceptive methods used after unprotected intercourse or potential contraceptive failure and before implantation. It interferes with follicular development, cervical mucus, sperm migration, corpus luteum activity and fertilization. It has no effect on established pregnancy.\textsuperscript{13}

- Table 5 outlines 3 emergency contraception options. Two regimens use oral medications and the other is a copper IUD.

- The World Health Organization reports a pregnancy rate of 1.1% with the levonorgestrel-only regimen (e.g. Plan B) compared with 3.2% for the Yuzpe regimen (estrogen/progestin pills).

- The copper IUD is more effective than either the levonorgestrel or Yuzpe methods.

- Effectiveness of EC \textit{declines with increasing delay of treatment following unprotected sexual intercourse}.
  - Levonorgestrel (e.g. Plan B) prevents 95% of pregnancies when taken \( \leq 24 \text{ hours} \) after intercourse, 85% within 25 to 48 hours, and 58% within 49 to 72 hours.
  - Corresponding figures for the Yuzpe regimen are 77%, 36%, and 31%.\textsuperscript{3}

- Of the hormonal emergency contraception regimens available in Canada, the levonorgestrel-only is the preferred.

- Emergency contraception may be made available to women with contraindications to the use of conventional oral contraceptive preparations because the duration of drug exposure is minimal.

- Repeated use of EC poses no known health risks and should not be a reason for denying access to treatment.

- Any regular contraceptive method can be started immediately after the use of levonorgestrel or combined estrogen/progestin emergency contraception methods.\textsuperscript{3}
  - Women should abstain from sexual intercourse or use barrier contraception for 7 days after levonorgestrel or combined estrogen/progestin emergency contraceptive regimens or until her next menses, whichever comes first.\textsuperscript{3}

- Evaluate for pregnancy if menses have not begun within 21 days following emergency contraception treatment.\textsuperscript{3}

\textbf{Indications for EC} \textsuperscript{47}

- 1 missed combined oral contraceptive pill in the first week
- 3 or more combined oral contraceptive pills missed in the 2nd or 3rd week
- 1 or more pills missed on Progestin only pill
- Depo-Provera® injection late by 2 weeks or more
- Failure to use contraceptive method
- Condom breakage or leakage
- Dislodgement of diaphragm or cervical cap or withdrawal of contraceptive vaginal ring
- Detachment of contraceptive patch
- Ejaculation on the external genitalia
- Mistimed fertility awareness
- Sexual assault when woman not using reliable contraception

Effect of Weight on EC Efficacy

- A Health Canada advisory, March 2014 instructed manufacturers to add new warnings to “morning after” emergency contraception as follows: “these pills are less effective in women weighing 165 to 176 pounds (75-80 kg), and are not effective in women over 176 pounds (80 kg). Women who weigh 165 pounds or more are advised to ask a health professional, such as a doctor or pharmacist, for advice on alternative methods of emergency contraception.”


- The copper intrauterine device is not affected by body weight and may be used in obese women.

- The SOGC provided the following comments regarding the Health Canada warning:
  - Women should be advised that scientific evidence shows that for any weight category, insertion of a copper intrauterine device for emergency contraception is more effective than any emergency contraceptive pill.
  - The basis for the warning is a 2011 study which found that levonorgestrel-only emergency contraception may be less effective in women with a body mass index of 25 to 29 and ineffective in women with a body mass index of 30 and over. However, further research is needed to confirm these findings.
  - Until further evidence is available, women with a body mass index of 30 and over who do not have access to or do not want a copper intrauterine device for emergency contraception should not be discouraged from using levonorgestrel-only emergency contraception, since it may still provide some benefit.

- The effect of weight on the efficacy of EC is considered an area of uncertainty and other agencies with updated statements agree with the SOGC statement. For example,
  - The European Medicines Agency conducted a review and concluded that emergency contraceptives can continue to be used in women of all weights, as the benefits are considered to outweigh the risks.
The Faculty of Sexual and Reproductive Healthcare (England) suggests more evidence is needed before specific recommendations can be made for obese women. They recommend the use of all EC methods in obese women and do not recommend increasing the dose of oral EC.  

Management of Adverse Effects to EC

- Vomiting within 2-3 hours of taking the pills: take another dose of EC as soon as possible.
- Routine use of antiemetics is not recommended but could be considered.\(^3\)
- To reduce the chance of nausea with the combined estrogen–progestin regimen, an antiemetic agent may be taken 1 hour before the first emergency contraception dose.\(^6\)

Potential New Emergency Contraceptive in Canada

- Ulipristal (UPA) in a single dose (30 mg) is approved by the FDA for emergency contraception and may be available in Canada in the future. UPA is a selective progesterone receptor modulator that can be taken up to 5 days after unprotected sexual intercourse.
- UPA and levonorgestrel ECs have similar effectiveness when taken within 3 days after unprotected sexual intercourse.
- UPA is more effective than the levonorgestrel formulation 3–5 days after unprotected sexual intercourse.\(^50\)

Table 5: Emergency contraceptive methods\(^5,47\)

<table>
<thead>
<tr>
<th>Class</th>
<th>Products</th>
<th>Contraindications</th>
<th>Adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper IUD</td>
<td>Copper-T IUD, Nova-T, Flexi-T, Mona Lisa Liberte</td>
<td>Absolute: pregnancy, undiagnosed vaginal bleeding, stenosed cervix, copper allergy, current PID or STI, cervical or endometrial cancer, copper allergy, inability to place or retain device. Relative: 2–28 days postpartum (to decrease risk of expulsion).</td>
<td>Major: salpingitis, uterine perforation, cervical perforation, endometrial embedding, menorrhagia, pain, infection, ectopic pregnancy.</td>
<td>Most effective if used within 5 days of unprotected intercourse.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>When the day of ovulation can be estimated, the Cu-IUD can be inserted beyond 5 days after sexual intercourse, as long as insertion does not occur &gt;5 days after ovulation</td>
</tr>
<tr>
<td>Oral Progestin only Pills</td>
<td>levonorgestrel 0.75 mg</td>
<td>Pregnancy</td>
<td>Nausea 23.1% Vomiting 5.6% Dizziness 11% Fatigue 17%</td>
<td>1.5 mg (2 × 0.75 mg tablets taken together) as soon as possible after unprotected intercourse (most effective if taken within 3 days).</td>
</tr>
<tr>
<td>Available in pharmacies without a prescription</td>
<td>Plan B, NorLevo, Next Choice, Option 2</td>
<td>Pregnancy</td>
<td></td>
<td>0.75 mg Q12H × 2 doses is equally effective.</td>
</tr>
<tr>
<td>Yuzpe (Off label use)</td>
<td>100 mcg of ethinyl estradiol + 500 mcg levonorgestrel q12h x 2 doses (Or comparable dose with available products)</td>
<td>Pregnancy Since duration of exposure brief the contraindications related to age or smoking do not apply to EC although the levonorgesterol-only EC option may be preferred in women with strong contraindications to estrogens.</td>
<td>Nausea 50% Vomiting 18% Dizziness 17% Fatigue 29% (may need an antiemetic)</td>
<td>Taken as soon as possible within 5 days of unprotected intercourse (most effective if taken within 3 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combined estrogen and progestin in 2 doses: 100 μg of ethinyl estradiol + 0.50 mg levonorgestrel q12h x 2 doses (as close as possible with available COC) Given as single dose not as effective as two doses</td>
</tr>
</tbody>
</table>

*PID = pelvic inflammatory disease (if at high risk, prophylaxis using one dose of azithromycin 1 g or doxycycline 200 mg may be prescribed)
Question 5: Is there evidence for other non-contraception benefits or harms of Combined Hormonal Contraceptives?

There are non-contraceptive benefits to CHC. In addition to benefits in patients with acne discussed on page 17 and the benefits in various cancers discussed below, the SOGC has listed the following benefits:

- Cycle regulation
- Decreased dysmenorrhea and menstrual flow
- Increased bone density
- Fewer perimenopausal symptoms
- Fewer ovarian cysts
- Decreased incidence or severity of premenstrual symptoms

Ovarian Cancer

- Use of COC is associated with a reduced risk of ovarian and endometrial cancer that continues for several decades after stopping.
- Reanalysis of individual patient data for 23,257 women with ovarian cancer compared with a control group of 87,303 without ovarian cancer from 45 epidemiological studies showed that
  - With every 5 years of use, there is approximately a 20% reduction in the risk of ovarian cancer.
  - After 15 years of use, risk was reduced by about half of those who had never used COC.

Colorectal Cancer

- A systematic review and meta-analysis published in 2009 reported that:
  - Women who had ever used oral contraceptives had a lower risk of colorectal cancer than those who have never used oral contraceptives.
  - The studies included were either case control or cohort, which have potential for bias.
  - Due to a lack of quality assessment and the relatively small number of women on which the primary analyses were based, the reliability of the conclusions is uncertain.
  - Duration of use did not have an effect on colorectal cancer risk although recent use (<10 years) had a lower risk than those whose last use was >10 years ago.
  - Women who had ever used OCs had a statistically significantly lower risk of:
    - Colorectal cancer (RR 0.81, 95% CI 0.72 to 0.92)
    - Colon cancer (RR 0.85, 95% CI 0.79 to 0.93)
    - Rectal cancer (RR 0.80, 95% CI 0.70 to 0.92)
  - These findings were similar to those derived from case-control and cohort studies separately; results for rectal cancer from cohort studies was not statistically significant.
Cervical Cancer

- The risk of cervical cancer **may increase** with duration of COC use.
- Reanalysis of individual data for 16,573 women with cervical cancer were compared with 35,509 without cervical cancer.
  - Current users of oral contraceptives showed **increased risk** of invasive cervical cancer with increasing duration of use:
    - > 5 years’ use vs. never use RR 1.90 (95% CI 1.69–2.13)
  - Risk returned to that of “never users” after 10 or more years.
  - Similar risk patterns were seen for invasive and in-situ cancer, and in high-risk human papillomavirus positive women.
  - The authors estimate that 10 years’ use of oral contraceptives from around age 20 to 30 years increases the cumulative incidence of invasive cervical cancer by age 50 from 3.8 to 4.5 per 1000 in more developed countries.\(^{54}\)
- The data discussed above was published in 2007. Use of the Human Papilloma Vaccine in more recent years may affect the strength of this association.

Breast Cancer

- A recent analysis of the risks of breast cancer associated with OC use summarized available evidence for the relative and absolute risk of breast cancer.\(^{55}\)
  - The Collaborative Group on Hormonal Factors and Breast Cancers (1996 meta-analysis of 54 case-control and cohort studies) reported that current use of OCs was associated with a 24% (95% CI 15-33%) elevation in risk of breast cancer that persisted for nearly a decade after discontinuation of treatment. Risk did not vary by estrogen dose. Absolute numbers of excess cases of breast cancer were estimated to range between 0.5 and 32 per 10,000 North American or European women who used combined OCs up to 10 years after stopping use.
  - A 2013 meta-analysis of observational studies reported similar increased relative risks for breast cancer for ever versus never use, OR of 1.08 (95% CI 1.00-1.17), which was not statistically significant after 5 years. Lifetime absolute increase in risk of breast cancer associated with ever versus never use of OCs was estimated at approximately 0.89%.
  - History of benign breast disease or a family history of breast cancer is not a contraindication to oral contraceptive use. See the Medical Eligibility charts\(^ {18}\) in Appendix 3.

Mortality

- A recent publication of the prospective, cohort, Nurses Health Study, reported on overall and cause specific mortality in 121,577 women followed from 1976 to 2012.\(^ {56}\)
  - 52% never used oral contraceptive, and 48% were ever users.
  - 31,286 deaths occurred during this time.
- No association was observed between ever use of oral contraceptives and all cause mortality.
- Violent or accidental deaths were more common among ever users (hazard ratio 1.20, 95% CI 1.04 to 1.37).
- Longer duration of use was more strongly associated with premature mortality due to breast cancer (trend P<0.0001) and decreased mortality rates of ovarian cancer (P=0.002).
- The authors state that results pertain to OCs with higher hormone doses rather than currently available lower estrogen and 3rd and 4th generation preparations.
APPENDIX 1: How to be reasonably certain that a woman is not pregnant

Available at http://www.cdc.gov/mmwr/pdf/rr/rr6205.pdf

A primary care provider can be reasonably certain that a woman is not pregnant if she has no symptoms or signs of pregnancy and meets any one of the following criteria:

- Is ≤ 7 days after the start of normal menses
- Has not had sexual intercourse since the start of last normal menses
- Has been correctly and consistently using a reliable method of contraception
- Is ≤ 7 days after spontaneous or induced abortion
- Is within 4 weeks postpartum
- Is fully or nearly fully breastfeeding (exclusively breastfeeding or the vast majority (≥ 85%) of feeds are breastfeeds, amenorrheic, and < 6 months postpartum
## APPENDIX 2: List of contraceptive products

### ORAL HORMONAL CONTRACEPTIVE PRODUCTS

<table>
<thead>
<tr>
<th>Generation of Progestin</th>
<th>Type of Pill</th>
<th>Estrogen Content</th>
<th>Progestin</th>
<th>Pack sizes (days)</th>
<th>Trade Name</th>
<th>Monthly Drug Cost $*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation progestin</td>
<td>Monophasic</td>
<td>EE 10 mcg x 24</td>
<td>NE 1 mg x 24 days</td>
<td>28</td>
<td>Lolo</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 20 mcg</td>
<td>NE 1 mg</td>
<td>21, 28</td>
<td>Minestrin1/20</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 30 mcg</td>
<td>NE 1.5 mg</td>
<td>21, 28</td>
<td>Loestrin 1.5/30</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 30 mcg</td>
<td>Ethynodiol diacetate 2 mg</td>
<td>21, 28</td>
<td>Demulin 30</td>
<td>15 (21) 16 (28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 35 mcg</td>
<td>NE 0.5mg</td>
<td>21, 28</td>
<td>Brevicon 0.5/35</td>
<td>13.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ortho 0.5/35</td>
<td>24.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 35 mcg</td>
<td>NE 1 mg</td>
<td>21, 28</td>
<td>Brevicon 1/35</td>
<td>13.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ortho 1/35</td>
<td>24.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Select 1/35</td>
<td>9.00</td>
</tr>
<tr>
<td></td>
<td>Biphasic</td>
<td>EE 35 mcg</td>
<td>NE 0.5mg x 12</td>
<td>21, 28</td>
<td>Synthecis</td>
<td>12.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NE 1 mg x 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triphasic</td>
<td>EE 35 mcg</td>
<td>NE 0.5 mg x 7, NE 0.75 mg x 7, NE 1 mg x 7</td>
<td>21, 28</td>
<td>Ortho 7/7/7</td>
<td>24.00</td>
</tr>
<tr>
<td></td>
<td>Progestin only</td>
<td></td>
<td>-</td>
<td>NE 0.35 mg</td>
<td>28</td>
<td>Micronor</td>
</tr>
<tr>
<td>2nd generation Progestin</td>
<td>Monophasic</td>
<td>EE 20 mcg</td>
<td>LN 0.1 mg</td>
<td>21, 28</td>
<td>Alesse</td>
<td>16.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alysenca</td>
<td>9.75</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Aviane</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Lutera</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>EE 30 mcg</td>
<td>LN 0.15 mg</td>
<td>21, 28</td>
<td>Min Ovral</td>
<td>16.25</td>
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<td></td>
<td></td>
<td></td>
<td>Portia</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Ovima</td>
<td>10.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 30 mcg</td>
<td>LN 0.15 mg</td>
<td>91 days</td>
<td>Seasonale</td>
<td>61.50/3 months</td>
</tr>
<tr>
<td></td>
<td>Biphasic</td>
<td>EE 30 mcg x 84</td>
<td>LN 0.15 mg x 84 days</td>
<td>91 days</td>
<td>Seasonique</td>
<td>61.50/3 months</td>
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<tr>
<td></td>
<td></td>
<td>EE 20 mcg x 7</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Triphasic</td>
<td>EE 30, 40,30 mcg 6, 5, 10 tabs</td>
<td>LN 0.05, 0.075, 0.125 mg x 6, 5, 10 tabs</td>
<td>21, 28</td>
<td>Triquilar</td>
<td>16.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 30 mcg</td>
<td>Desogestrel 0.15 mg</td>
<td>21, 28</td>
<td>Apri</td>
<td>10.50</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
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<td>Mirvala</td>
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<td>Reclipsen</td>
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<td>Marvelon</td>
<td>20.25</td>
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<td></td>
<td>EE 35 mcg</td>
<td>Norgestimate 0.25 mg</td>
<td>21, 28</td>
<td>Cyclen</td>
<td>24.00</td>
</tr>
<tr>
<td></td>
<td>Triphasic</td>
<td>EE 25 mcg</td>
<td>Desogestrel 7 tabs each of 0.1, 0.125, 0.15 mg</td>
<td>21, 28</td>
<td>Linessa</td>
<td>17.00</td>
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<tr>
<td></td>
<td></td>
<td>EE 25 mcg</td>
<td>Norgestimate 7 tabs each of 0.18, 0.215, 0.25 mg</td>
<td>21, 28</td>
<td>Tri-Cyclen Lo</td>
<td>16.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tricira Lo</td>
<td>9.50</td>
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<tr>
<td></td>
<td></td>
<td>EE 35 mcg</td>
<td>Norgestimate 7 tabs each of 0.18 mg, 0.215 mg, 0.25 mg</td>
<td>21, 28</td>
<td>Tri-Cyclen</td>
<td>24.00</td>
</tr>
<tr>
<td></td>
<td>Drosipirenone containing</td>
<td>Monophasic</td>
<td>EE 20 mcg</td>
<td>Drosipirenone 3 mg</td>
<td>28 day</td>
<td>Yaz, Yaz plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 active, 4 placebo (Yaz) or 4 Levomefolate 0.45 mg</td>
<td>Mya</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EE 30 mcg</td>
<td>Drosipirenone 3 mg</td>
<td>21 and 28</td>
<td>Yasmin</td>
<td>13.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Zarah</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Zamine</td>
<td>9.00</td>
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</tbody>
</table>

EE = Ethinyl Estradiol; NE = Norethindrone; LN = Levonorgestrel

*McKesson Wholesale cost, rounded to $0.25 without dispensing fee (June 25, 2015)
# Products Indicated for Acne Vulgaris and/or Contraception

<table>
<thead>
<tr>
<th>Estrogen Content</th>
<th>Progestin</th>
<th>Pack sizes (days)</th>
<th>Trade Name</th>
<th>Monthly Drug Cost $*</th>
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</thead>
<tbody>
<tr>
<td><strong>Officially indicated for contraception and acne vulgaris</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE 20 mcg</td>
<td>LN 0.1 mg</td>
<td>21,28</td>
<td>Alesse</td>
<td>16.25</td>
</tr>
<tr>
<td>EE 35 mcg</td>
<td>Norgestimate 7 tabs each 0.18 mg, 0.215 mg, 0.25 mg</td>
<td>21, 28</td>
<td>Tri-Cyclen</td>
<td>24.00</td>
</tr>
<tr>
<td>EE 20 mcg</td>
<td>Drospirenone 3 mg Plus: Levomelofol 0.45 mg</td>
<td>28</td>
<td>Yaz</td>
<td>17.25</td>
</tr>
<tr>
<td>EE 30 mcg</td>
<td>Drospirenone 3 mg</td>
<td>21, 28</td>
<td>Yasmim</td>
<td>13.25</td>
</tr>
<tr>
<td>EE 35 mcg</td>
<td>Cyproterone 2 mg</td>
<td>21</td>
<td>Diane 35</td>
<td>37.25</td>
</tr>
<tr>
<td><strong>Officially indicated for acne</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE 20 mcg</td>
<td>LN 0.1 mg</td>
<td>21</td>
<td>Plan B, NorLevo, Next Choice, Option 2</td>
<td>18.25</td>
</tr>
<tr>
<td>EE 35 mcg</td>
<td>Cyproterone 2 mg</td>
<td>21</td>
<td>5-10 years depending on IUD</td>
<td>18.25</td>
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</table>

**Non-Oral Hormonal Contraceptive Products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Trade Name</th>
<th>Estrogen Content</th>
<th>Progestin</th>
<th>Time frame</th>
<th>Cost $*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transdermal Patch</strong></td>
<td>Evra</td>
<td>EE 0.60 mg</td>
<td>Norelgestromin 6.0 mg</td>
<td>1 patch applied each week on the same day x 3 weeks. Week 4 is patch free</td>
<td>18 per 3 patches</td>
</tr>
<tr>
<td><strong>Vaginal Ring Slow Release</strong></td>
<td>Nuvaring</td>
<td>EE 2.6 mg</td>
<td>Etonogestrel 11.4 mg</td>
<td>Insert new ring and retain x 3 wks then remove for 1 week.</td>
<td>16.75/ring</td>
</tr>
<tr>
<td><strong>Progestin Injection</strong></td>
<td>Depo-Provera</td>
<td></td>
<td>Medroxyprogesterone</td>
<td>150 mg IM every 3 months (every 13 weeks)</td>
<td>30 per 3 months</td>
</tr>
<tr>
<td><strong>Levonorgestrel Containing IUD</strong></td>
<td>Mirena</td>
<td>LN 52 mg</td>
<td></td>
<td>5 years</td>
<td>367</td>
</tr>
<tr>
<td></td>
<td>Jaydess</td>
<td>LN 13.5 mg</td>
<td></td>
<td>3 years</td>
<td>294</td>
</tr>
<tr>
<td><strong>Copper IUD</strong></td>
<td>Nova T</td>
<td></td>
<td></td>
<td>5-10 years depending on IUD</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>Flexi T</td>
<td></td>
<td></td>
<td></td>
<td>73-83</td>
</tr>
<tr>
<td></td>
<td>Mona Lisa</td>
<td></td>
<td></td>
<td></td>
<td>49-65</td>
</tr>
<tr>
<td></td>
<td>Liberte</td>
<td></td>
<td></td>
<td></td>
<td>55-64</td>
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</table>

**Emergency Contraception Options**

<table>
<thead>
<tr>
<th>Product</th>
<th>Trade name</th>
<th>Cost (McKesson Wholesale)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IUD</strong></td>
<td>Nova-T</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>Flexi-T</td>
<td>73-83</td>
</tr>
<tr>
<td></td>
<td>Mona Lisa</td>
<td>49-65</td>
</tr>
<tr>
<td></td>
<td>Liberte</td>
<td>55-64</td>
</tr>
<tr>
<td><strong>Progestin only Pill</strong></td>
<td>Plan B, NorLevo, Next Choice, Option 2</td>
<td>18.25</td>
</tr>
<tr>
<td><strong>Levonorgestrel 0.75 mg x 2 tablets No prescription needed</strong></td>
<td>18.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.50</td>
<td></td>
</tr>
<tr>
<td><strong>Combination Oral Contraceptive Pills (Yuzpe method)</strong></td>
<td>100 mcg of Ethinyl Estradiol + 500 mcg Levonorgestrel q12h x 2 doses</td>
<td>9.75 to 16.25</td>
</tr>
<tr>
<td>Example: 5 tablets containing EE 20 mcg and LN 100 mcg q12h x 2 doses e.g., Alesse, Alyesena etc.</td>
<td>9.75 to 16.25</td>
<td></td>
</tr>
</tbody>
</table>

EE = Ethinyl Estradiol; NE = Norethindrone; LN = Levonorgestrel; * McKesson Wholesale cost without dispensing fee June 25, 2015
APPENDIX 3: Medical eligibility for initiating contraception

Medical Eligibility for Initiating Contraception: Absolute and Relative Contraindications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Qualifier for condition</th>
<th>Estrogens/ progesterin pill, patch, ring</th>
<th>Progesta- only pill</th>
<th>Progesta- only injection</th>
<th>Progesta- only implant</th>
<th>Progesta- only sub</th>
<th>Copper IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 18</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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<tr>
<td></td>
<td>18-49</td>
<td>1</td>
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<td>1</td>
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</tr>
<tr>
<td></td>
<td>&gt; 45</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Anemia</td>
<td>Thalassemia</td>
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<td>Sickle cell disease</td>
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<tr>
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<td>Non-deficiency anemia</td>
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<td>Gastrectomy</td>
<td>Stomach restrictive procedures, including lap band</td>
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<tr>
<td>Malabsorptive procedures, including gastric bypass</td>
<td>Patch or ring: PPI, 1</td>
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<td>Breast cancer</td>
<td>Family history of cancer</td>
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<td>In past, no evidence of disease for x years</td>
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<td>Breast problems, benign</td>
<td>Undiagnosed mass</td>
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<td>Benign breast disease</td>
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<td>Cervical cancer and pre-cancerous changes</td>
<td>Cervical intraepithelial neoplasia</td>
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<td>Cancer, awaiting treatment</td>
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<td>Cervical ectropion</td>
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<td>Depression</td>
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<td>Diabetes mellitus (DM)</td>
<td>Gestational DM in past</td>
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<td>DM without vascular disease</td>
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<td>DM with end-organ damage or &gt; 20 years duration</td>
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<td>Drug interactions</td>
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<td>Protease inhibitors</td>
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<td>Antiretrovirals: phenytoin, carbamazepine, barbiturates, pemetrexed, ertapenem, lansoprazole</td>
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<td>Lamotrilone alone (Lamotrilone/converted dose does not interact with hormones)</td>
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<td>Rifampin/rifabutin</td>
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<td>ALL OTHER ANTIBIOTICS &amp; ANTIFUNGALS</td>
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<td>Gallbladder disease</td>
<td>Asymptomatic gallstones or s/p cholecystectomy</td>
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<td>Symptomatic gallstones, without cholecystectomy</td>
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<td>Pregnancy-related cholestasis in past</td>
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<td>Hormone-related cholestasis in past</td>
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<td>Without auras, age &lt; 35</td>
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<td>Without auras, age &gt; 35</td>
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<td>Condition</td>
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<td>Progestin-only injection</td>
<td>Progestin-only implant</td>
<td>Progesterone IUD</td>
<td>Copper IUD</td>
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<td>During prior pregnancy only – now resumed</td>
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<td>&gt; 6 weeks postpartum</td>
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<td>Uterine fibroids</td>
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October 2014
APPENDIX 4: The International Headache Society diagnostic criteria for migraine

Without Aura
A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 h (untreated or unsuccessfully treated)
C. Headache with at least 2 of the following:
   — Unilateral location
   — Pulsating quality
   — Moderate or severe pain intensity
   — Aggravation by or causing avoidance of routine physical activity (e.g. walking)
D. During headache, at least 1 of the following is present:
   — Nausea and/or vomiting
   — Photophobia and phonophobia
E. Not attributed to another disorder

With Aura*
A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of at least 1 of the following, but no motor weakness:
   1. Fully reversible visual symptoms including positive features (e.g. flickering lights, spots, or lines) and/or negative features (i.e., loss of vision)
   2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
   3. Fully reversible dysphasic speech disturbance
C. At least 2 of the following characteristics:
   1. Homonymous visual symptoms and/or unilateral sensory symptoms
   2. At least 1 aura symptom develops gradually over ≥ 5 min, and/or different aura symptoms occur in succession over ≥ 5 min
   3. Each symptom lasts ≥ 5 minutes and ≤ 60 min
D. Headache fulfilling criteria B-D for migraine without aura begins during the aura or follows aura within 60 min
E. Not attributed to another disorder

*Other less common types of migraine with aura include typical aura with non-migraine headache, typical aura without headache, familial hemiplegic migraine, and others.
References:


