Evidence report for hormonal treatment of endometriosis

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Marty Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

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Evidence report for hormonal treatment of endometriosis

Scoping

Prepared by EBSCO Information Services

October 30, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Abbreviations

General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IQR – interquartile range
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NMA – network meta-analysis
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SD – standard deviation
SE – standard error
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

Abbreviations specific to this report that may appear in this report

COC, COCP – combination oral contraceptive / combination oral contraceptive pill
DVT – deep venous thrombosis
GnRH – gonadotropin-releasing hormone (sometimes also spelled “gonadotrophin”)
GnRHa – gonadotropin-releasing hormone agonist (sometimes also spelled “gonadotrophin”)
IM, i.m. – intramuscular
IU, i.u. – intrauterine
IUD – intrauterine device
IUS – intrauterine system
LNG – levonorgestrel
OC – oral contraceptive
PE – pulmonary embolism
QoL, QOL – quality of life
SC, s.c., subQ – subcutaneous
SF-12 – 12-Item Short Form Survey (a modified version of the 36-Item Short Form Survey)
SF-36 – 36-Item Short Form Survey
VAS – visual analog scale
VTE – Venous thromboembolism

Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Scoping was completed on October 30, 2019.

Results – Criteria Selection for Critical Appraisal

Population:

Inclusion criteria

Women at childbearing age with confirmed or suspected endometriosis of any stage, recurrence status, or severity who are having pain.

Exclusion criteria

We will exclude studies with a primary focus on an endometriosis-related concern other than pain, such as subfertility; populations who have symptoms that could be due to endometriosis, but without suspicion or confirmation of endometriosis as the underlying etiology (eg, women with undifferentiated chronic abdominopelvic pain or dysmenorrhea); and studies in post-menopausal women.

Options:

Symptomatic treatment alone (no hormonal therapy)

Symptomatic treatment may be used with any other option. This option will describe basic non-hormonal symptomatic treatment choices, focusing on non-steroidal anti-inflammatory medications (NSAIDs) as a class (which includes medications like ibuprofen and naproxen).

The evidence for analgesics among women with endometriosis is of very low quality, consisting of one small crossover randomized trial (n = 24) comparing naproxen sodium vs. placebo, which found no clear difference (but with wide CIs) for the outcomes overall pain relief, unintended effects, or need for additional analgesia (Brown 2017). Despite the scarce evidence on analgesics in women with endometriosis, guidelines have recommended that patients consider them to reduce pain (NICE 2017; Dunselman 2014).

Due to the very limited evidence base but common use of these medications, we will include descriptive responses for all FAQs in this evidence report for this option. We will also treat this option as a functional comparator for the hormonal options where applicable. There is insufficient evidence to know how NSAIDs alone might fare versus hormonal therapy alone. However, in head-to-head trials of different hormonal treatments (+/- a placebo-controlled group) or trials of hormonal treatment versus a placebo-controlled group, NSAIDs may have been used by women as background therapy, irrespective of whether the trial explicitly stated such. We consider this probable, given the ethical problems surrounding approval of a trial that strictly disallows background symptomatic therapy during trials of hormonal therapies. Therefore, as an example, a trial of a hormonal therapy vs. placebo may be better thought of as a trial of hormonal therapy + background symptomatic therapy as desired vs. placebo + background symptomatic therapy as desired.

Combined estrogen plus progestogen pill

Traditional use of this intervention involves taking 1 tablet every day for 3 weeks and then taking a break for a week (which may involve taking inert pills with or without iron). Alternatively, the patient may take a week-long break after 3 months of treatment (“tricycling”), or not take a break at all (“long cycle” or “continuous” therapy).

Although existing evidence is specific to the cyclic use of the combined oral contraceptive pill, continuous use and tricycling are also commonly used in clinical practice and considered to be effective. All forms of combined oral contraceptives will be included without distinguishing subtypes of combined oral contraceptives by scheduling variations, dosing, or specific medications.

Progestogen pill

This intervention involves taking 1 tablet every day with no breaks.

All oral progestogen formulations will be considered without distinguishing subtypes by dosing or specific medication.

Progestogen injection/depot

This intervention involves having a progestogen injection into the muscle of the bottom or shoulder every 3 months.

This was not a previously scoped option. This option will be considered initially in case there are important differences compared to other hormonal therapies. If no differences are found, this option may not be carried forward to Evidence Synthesis.

Progestogen intrauterine system

This intervention involves insertion by a nurse or doctor of a small plastic device that releases progestogen into the womb. It requires removal or replacement after 3 to 5 years.

All formulations will be considered without distinguishing subtypes by brand or specific medication.

Progestogen implant/subcutaneous

This intervention involves injection of a small implant under a woman's skin on the inner side of her upper arm. It requires removal or replacement after 3 years.

This was not a previously scoped option. This option will be considered initially in case there are important differences compared to other hormonal therapies. If no differences are found, this option may not be carried forward to Evidence Synthesis.

Gonadotropin releasing hormone analogue/agonist injection/depot

This intervention involves an injection of a GnRH analogue. How often the injection occurs may vary, but it is common to get injections monthly or every three months depending on the injection and dose used. For instance, leuprolide may be given monthly at a lower dose or every three months at a higher dose, whereas goserelin is typically given monthly.

All formulations will be considered without distinguishing subtypes by dosing or specific medication.

Outcomes:

Where outcomes will be answered with systematic searches, critical appraisal, and evidence synthesis, we will state the intended approach after we state the outcome(s) of interest for that FAQ. For example, we might say: "The outcome of interest is all-cause mortality. We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist or meta-analysis is not the most appropriate method of synthesis." Otherwise, where we say: "We will include a description of", "We will include descriptive responses", or something similar, we will answer the FAQ with descriptive responses, which do not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 1: What does the treatment involve?

We will include a description of the treatment or procedure, including a description of the delivery method (eg, pill, implant) and/or frequency of dosing, as relevant (similar to statements noted in the description of options above). We will also include a description of the impact on menstrual periods, contraceptive effects, and implications for stopping use (eg, how implants are removed and that time may be needed for effects to wear off after discontinuation, including effect on subsequent fertility).

FAQ 2: Will my pain get better?

The outcome of interest is pain relief. We will focus on measure of overall pain, but we will consider specific pain subscales for the types of pain most often reported by women with endometriosis (eg, dysmenorrhea [painful menstruation], dyspareunia [painful intercourse], and non-menstrual pelvic pain) if sufficient evidence is available.

We will obtain effect estimates from systematic reviews/meta-analyses and/or network meta-analyses of randomized, controlled trials.

FAQ 3: Will my quality of life get better?

The outcome of interest is quality of life reported on any scale.

We will obtain effect estimates from systematic reviews/meta-analyses and/or network meta-analyses of randomized, controlled trials.

It appears evidence may be insufficient for endometriosis symptoms other than pain, such as nausea or fatigue. However, if we find evidence pertaining to such symptoms during our systematic searches to address the FAQs on pain and quality of life, we will include summaries of this evidence as part of addressing the FAQ on quality of life.

FAQ 4: What are the side effects or risks?

Because specific adverse effects vary depending on option in question, because some of the options being considered are broad medication classes rather than a single medication (e.g., combination oral contraceptive pills is a category that contains numerous different estrogens and progestogens, both in type and dose), and because some of the options being considered may not have been studied against each other in a head-to-head fashion, we plan to use discontinuation of treatment due to adverse events as our quantified outcome. This outcome is generalizable and accounts for the severity of an adverse effect (ie, that it required stopping treatment). In other words, this outcome allows women to see an outcome that is common to all options while also giving women an idea of how bothersome side effects may be, which may facilitate decision-making among the options. This is consistent with major

guidelines addressing this clinical question (NICE 2017). However, we will also include a description of common specific side effects that may occur, such as acne, increased blood pressure, breast tenderness, cysts on ovaries that are painful but temporary, hair loss, headaches, mood changes, nausea, and sex drive decrease.

In addition, we will consider the risks of deep vein thrombosis/venous thromboembolism and breast cancer.

We will obtain effect estimates from systematic reviews/meta-analyses and/or network meta-analyses of randomized, controlled trials.

Brown J, Crawford TJ, Allen C, Hopewell S, Prentice A. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev. 2017 Jan 23;1:CD004753. doi: 10.1002/14651858.CD004753.pub4. PubMed

Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W; European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014 Mar;29(3):400-12. doi: 10.1093/humrep/det457. Epub 2014 Jan 15. PubMed

National Institute for Health and Care Excellence (NICE). Endometriosis: diagnosis and management. NICE Guideline No. 73. 2017 Sep. PubMed

Evidence report for hormonal treatment of endometriosis

Evidence Synthesis

Prepared by EBSCO Information Services

December 2, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, FAMIA, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summary/-ies will be given.

For each FAQ for which evidence synthesis or processing is considered, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. For each outcome, Evidence Synthesis Process tables will then articulate the method selected for evidence synthesis and justification of that method. We will do this for the effect estimate (i.e., answering the question "Is there a difference between the intervention and comparator?") and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is "What will happen with this option?" rather than "How do things change with this option?") the Evidence Synthesis Process tables will be extended to include the method to produce noncomparative responses.

For summary statements representing a plain language summary of evidence appraisal and synthesis

We will include the following 2 items immediately after the summary statement as a parenthetical, regardless of whether they occur in the Summary of Findings section or the individual FAQs in the body of the Evidence Synthesis document:

- our certainty in the summary statement (categorized as High, Moderate, Low, or Very low), and
- the number and type of studies informing the statement, as well as a label for the studies in "[Author] [Year]" format.

If the study informing the summary statement is a systematic review and meta-analysis, then unless there are compelling reasons to proceed in a different manner, we will cite the systematic review and meta-analysis as the source. We will do this even if the result on which our summary statement is based comes from a subset of studies in that systematic review and meta-analysis (e.g., a meta-analysis of 5 out of 10 studies, because only 5 of the 10 reported on the outcome of interest). If EBSCO Information Services conducts its own meta-analysis of studies to inform a summary statement, we will list the individual studies.

For summary statements representing a plain language summary of descriptive sources

Certainty rating and provision of details about contributing studies do not apply. Accordingly, we will not include a parenthetical at the end of the summary statement. However, when descriptive summaries appear in the Summary of Findings section, we will include a general parenthetical citation of the references we consulted. We will place this at the end of the relevant FAQ in the Summary of Findings section. For summary statements occurring in the body of the Evidence Synthesis document, we will provide this general parenthetical citation as part of the longer descriptive summary component that precedes the simplified summary statement.

Results – Summary of Findings

FAQ 1: What does the treatment involve?

Symptomatic treatment alone (no hormonal therapy)

You can use things like heat at painful areas. You can also take medicines that do not have hormones in them. This includes medicines like ibuprofen or naproxen. If the pain is very bad, you might try tramadol or opioids. However, tramadol and opioids are not used unless pain is not relieved enough with other treatments. Medications that do not have hormones in them can be used with medications that do have hormones in them.

Combined estrogen plus progestogen pill (combined oral contraceptives)

How will I take this treatment?

You will take 1 pill every day that has 2 hormones in it. Every month or every 3 months, you might have a week where you stop taking the pill with hormones in it. During this week, you might take a different pill or no pill at all. After that week, you will start taking the pill with hormones again. You can stop taking this medicine at any time.

Will it change my menstrual period?

When a woman is first using this medicine, she may have some spotting or bleeding at random times. This might last for a couple of months. If women have weeks where they stop taking the pill with hormones in it, they will usually have a menstrual period. But it may be shorter and lighter than usual.

Will it change my ability to get pregnant?

This kind of medicine is also used by women who do not want to get pregnant. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. These things will likely happen quickly if you stop using this medicine. However, for a small number of women, there might be a delay.

Progestogen pill

How will I take this treatment?

You will take 1 pill every day that has 1 hormone in it. You can stop using it at any time.

Will it change my menstrual period?

When a woman is using this medicine, she may have some spotting or bleeding at random times. This might happen most when she is first starting the medicine. If a woman has bleeding, it may be shorter and lighter than her normal menstrual period. Some women have no bleeding.

Will it change my ability to get pregnant?

This kind of medicine is also used by women who do not want to get pregnant. One of the progestogen pills is called dienogest, and it is not used to block pregnancy. Women taking dienogest should always use something that blocks pregnancy without hormones, like a condom. If you stop using this kind of medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. These things will likely happen quickly if you stop using this medicine.

Progestogen injection/depot

How will I take this treatment?

You will get an injection of a hormone every 3 months. The injection will be in your shoulder or bottom. Once the injection has been given, it cannot be removed or reversed.

Will it change my menstrual period?

At first, women may have spotting, bleeding at random times, or bleeding that lasts longer than usual. However, after women have been using this medicine for about a year, most have no bleeding.

Will it change my ability to get pregnant?

This medicine is also used by women who do not want to get pregnant. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. However, this can take up to a year for some women.

Progestogen intrauterine system

How will I take this treatment?

You will have a small device shaped like a "T" inserted into your uterus. This can be done in the office and does not take long. The device slowly releases a hormone and lasts for 3 to 5 years. You can have it removed at any time, but it must be done by a health care professional.

Will it change my menstrual period?

At first, women may notice they have more pain and lighter or heavier bleeding with their menstrual period. Some women may have spotting or bleeding at random times. If these things happen, they usually get better within 3 to 6 months. Some women stop having any menstrual bleeding.

Will it change my ability to get pregnant?

This medicine is also used by women who do not want to get pregnant. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. These things will likely happen quickly if you stop using this medicine.

Progestogen implant/subcutaneous

How will I take this treatment?

You will have a rod about the size of a matchstick inserted under the skin of your inner arm. This can be done in the office and does not take long. The rod slowly releases a hormone and lasts for 3 years. You can have it removed at any time, but it must be done by a health care professional.

Will it change my menstrual period?

Women may have lighter or heavier bleeding with their menstrual period, or they may stop having menstrual periods. Some women may have spotting or bleeding at random times. Whatever happens during the first 3 months of use often continues for the rest of the time a woman uses this medicine.

Will it change my ability to get pregnant?

This medicine is also used by women who do not want to get pregnant. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. These things will likely happen quickly if you stop using this medicine.

Gonadotropin releasing hormone analogue/agonist injection/depot

How will I take this treatment?

You will get an injection of a medication that acts like a hormone, and it is often given every month or every 3 months. Once you get the injection, it cannot be reversed or removed.

Will it change my menstrual period?

After the first two weeks, women may have spotting or bleeding for up to 5 days. Most women have no bleeding after 2 months.

Will it change my ability to get pregnant?

Women using this medicine are unlikely to get pregnant. However, if a woman gets pregnant while using this medicine, the medicine can hurt the baby. Because of this, your health care professional may suggest using extra methods to make sure you do not get pregnant while using this medicine. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. However, this may take up to 6 to 10 weeks.

(Certainty ratings for descriptive responses not applicable; sources contributing to the above descriptive responses include HHS 2019, NICE 2017, and Wood nd)

FAQ 2: Will my pain get better?

Symptomatic treatment alone (no hormonal therapy)

Women who treat their symptoms without hormones may notice their pain get better, get worse, or stay about the same. This depends on the treatments a woman uses. Options include heating pads or medication like ibuprofen or naproxen. If the pain is really bad, tramadol or opioids might be used, but they are used for as short a time as possible. (Certainty rating not applicable)

Effects of hormonal medical treatments vs. placebo/expectant management or another hormonal treatment

Note: Because the evidence synthesis statement for each of the hormone-based options is essentially the same, we present each of the evidence synthesis statements under this single heading; the only difference in the evidence synthesis statements is the certainty rating for some of the options, which results in some options saying "may" and other options saying "might".

Women who take a combination oral contraceptive may have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Moderate certainty based on 2 systematic reviews [Brown 2018, NICE 2017])

Women who take a progestogen-only oral contraceptive might have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Very low certainty based on 1 systematic review [NICE 2017])

Women who use a progestogen injection might have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Very low certainty based on 1 systematic review [NICE 2017])

Women who use a progestogen intrauterine system may have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Moderate certainty based on 2 systematic reviews [Grandi 2019, NICE 2017])

Women who use a progestogen implant might have more improvement in their pain compared to treating symptoms without hormones. (Very low certainty based on 1 systematic review [NICE 2017])

Women who use an injection of a gonadotropin-releasing hormone agonist might have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Low certainty based on 1 systematic review [NICE 2017])

The different hormone treatments might all decrease pain by a similar amount. (Very low certainty based on 1 systematic review [NICE 2017])

FAQ 3: Will my quality of life get better?

Symptomatic treatment alone (no hormonal therapy)

Women who treat their symptoms without hormones may notice their quality of life get better, get worse, or stay about the same. This depends on the treatments a woman uses. Options include heating pads or medication like ibuprofen or naproxen. If the pain is really bad, tramadol or opioids might be used, but they are used for as short a time as possible. (Certainty rating not applicable)

Effects of hormonal medical treatments vs. placebo/expectant management or another hormonal treatment

Note: Because we give a single evidence synthesis statement for all the hormone-based options, we present the evidence synthesis statement under this single heading.

Women using a hormone treatment may have an improvement in their quality of life compared to what it was before treatment. However, some women may not have any noticeable improvement. (Very low certainty based on 3 systematic reviews [Grandi 2019, Jensen 2018, NICE 2017]) Symptom treatment without hormones may also improve a woman's quality of life. (Certainty rating not applicable) We do not have enough research to know how treatments compare to each other. (Insufficient evidence based on 3 systematic reviews [Grandi 2019, Jensen 2018, NICE 2017])

FAQ 4: What are the side effects or risks?

Note: We scoped withdrawal due to adverse effects as an outcome of interest for this FAQ; however, we found the underlying evidence to be too unreliable to include in evidence synthesis statements.

Option-specific adverse events

Symptomatic treatment alone (no hormonal therapy)

Side effects depend on what kind of symptomatic treatment you use.

- Using heat at painful areas does not usually have any side effects.
- Medications like ibuprofen and naproxen can cause upset stomach and heart burn.
- Tramadol and opioids can be addictive, and they can also cause fatigue, dizziness, constipation, upset stomach.

Combined estrogen plus progestogen pill (combined oral contraceptives)

Side effects may include:

- headache
- feeling hungry more often
- weight gain
- nausea
- fluid buildup and bloating
- mood changes
- your breasts feeling tender

Depending on the specific medicine used, women may notice new or worsening acne, or they may notice their acne gets better.

If you have side effects that bother you, trying a different type of pill may help decrease side effects or make them more tolerable.

Progestogen pill

Side effects may include:

- headache
- feeling hungry more often
- nausea
- fluid buildup and bloating
- mood changes
- your breasts feeling tender

Depending on the specific medicine used, women may notice new or worsening acne, or they may notice their acne gets better.

If women take dienogest, they may also notice symptoms like hot flashes and weight gain. This may be due to how dienogest works.

If you have side effects that bother you, trying a different type of pill may help decrease side effects or make them more tolerable.

Progestogen injection/depot

Side effects may include:

- acne
- hair loss
- feeling tired or dizzy
- stomach pain
- headache
- weight gain
- mood changes

When this medication is used for long periods of time, some women's bones may get thinner. If this happens, the bones can usually go back to normal health when a woman stops using this medication.

Progestogen intrauterine system

Side effects may include:

- acne
- stomach pain
- nausea
- headache
- your breasts feeling tender

Some woman get collections of fluid on their ovaries while taking this medication. These are called ovarian cysts. If this happens, the most common symptom is pain in your lower stomach or pelvis. The cysts usually go away without specific treatment.

Progestogen implant/subcutaneous

Side effects may include:

- acne
- stomach pain
- nausea
- headache
- weight gain
- mood changes
- your breasts feeling tender

Gonadotropin releasing hormone analogue/agonist injection/depot

Many of the side effects are like what a woman might feel when she is going through menopause.

Side effects may include:

- hot flushes and night sweats
- vaginal dryness or irritation
- your breasts getting smaller
- difficulty sleeping
- mood changes
- less interest in sex

- acne
- muscle pain
- dizziness
- nausea and vomiting
- headaches
- fluid buildup

(Certainty rating not applicable; sources contributing to this descriptive response include DynaMed 2018/2019, HHS 2019, NICE 2017, and Wood nd)

Venous thromboembolism

Symptomatic treatment alone (no hormonal therapy)

Of 1,000 women who treat their symptoms without hormones, about 3 (0.3%) may get a blood clot over the next 10 years. (Low certainty based on 1 cohort study [Lidegaard 2009])

Combined estrogen plus progestogen pill (combined oral contraceptives)

Of 1,000 women who take a combined oral contraceptive pill, about 5 to 11 (0.5% to 1.1%) may get a blood clot over the next 10 years depending on the type of combined oral contraceptive a woman uses. (Low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review and meta-analysis of observational studies [Dragoman 2018])

Progestogen pill

Of 1,000 women who take a progestogen-only pill, about 3 (0.3%) may have a blood clot over the next 10 years. (Very low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review [Tepper 2016])

Progestogen injection/depot

Of 1,000 women who use a progestogen injection, about 7 to 9 (0.7% to 0.9%) may have a blood clot over the next 10 years. (Very low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review [Tepper 2016])

Progestogen intrauterine system

Of 1,000 women who use a progestogen intrauterine system, about 3 (0.3%) may have a blood clot over the next 10 years. (Very low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review [Tepper 2016])

Progestogen implant/subcutaneous

Of 1,000 women who use a progestogen implant, about 4 to 6 (0.4% to 0.6%) may have a blood clot over the next 10 years. (Very low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review [Tepper 2016])

Gonadotropin releasing hormone analogue/agonist injection/depot

Of 1,000 women who use an injection of a gonadotropin-releasing hormone agonist, about 3 (0.3%) may get a blood clot over the next 10 years. (Low certainty based on 1 cohort study [Lidegaard 2009])

Breast cancer

Symptomatic treatment alone (no hormonal therapy)

Of 1,000 women who treat their symptoms without hormones, about 6 (0.6%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Combined estrogen plus progestogen pill (combined oral contraceptives)

Of 1,000 women who take a combined oral contraceptive pill, about 7 (0.7%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Progestogen pill

Of 1,000 women who use a progestogen pill, 6 (0.6%) to 7 (0.7%) may get breast cancer over the next 10 years. The risk may be 6 out of 1,000 (0.6%) if the progestogen is norethisterone or desogestrel and 7 out of 1,000 (0.7%) if the progestogen is levonorgestrel. (Low to Very low certainty based on 1 cohort study [Mørch 2017])

Progestogen injection/depot

Of 1,000 women who use a progestogen injection, about 6 (0.6%) may get breast cancer over the next 10 years. (Very low certainty based on 1 cohort study [Mørch 2017])

Progestogen intrauterine system

Of 1,000 women who use a progestogen intrauterine system, about 7 (0.7%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Progestogen implant/subcutaneous

Of 1,000 women who use a progestogen implant, about 6 (0.6%) may get breast cancer over the next 10 years. (Very low certainty based on 1 cohort study [Mørch 2017])

Gonadotropin releasing hormone analogue/agonist injection/depot

Of 1,000 women who use an injection of a gonadotropin-releasing hormone agonist, about 6 (0.6%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Search Summary

Search summary:

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed)	39	2
2nd-round (Systematic review searches)	91	8
3rd-round (Original article searches)	43	0
4th-round (Citation tracing)	6	6
Total	*179*	*16*†

* Number shown is after deduplication

† For ease of comprehension and efficiency, we do not include all references in Critical Appraisal or Evidence Synthesis. This is due to sources being functionally supplanted by more current sources, sources giving consistent findings with other sources, sources being consulted to clarify details in other sources, and the like.

	Articles selected for evaluation (Author Year)
Systematic reviews	9 (Bergendal 2009*, Brown 2018†, Dragoman 2018‡, Grandi 2019§, Jensen 2018, NICE 2017, Oedingen 2018¶, Samson 2016, Tepper 2016)
Randomized, controlled trials	2 (Harada 2008, Harada 2017)**
Other article types	5 (Backman 2005††, Dinger 2011§, Lidegaard 2009, Mørch 2017, Soini 2014 [all observational studies])

* All 5 studies included in Bergendal 2009 are also included in the more current Tepper 2016, so we do not summarize/appraise or utilize Bergendal 2009 in this evidence report other than to note it is functionally supplanted by Tepper 2016.

† Systematic review of randomized, controlled trials

‡ Systematic review of observational studies

§ Systematic review of randomized, controlled trials and observational studies

¶ Oedingen 2018's results are consistent with Dragoman 2018's results, so we do not summarize/appraise or utilize Oedingen 2018 in this evidence report other than noting its consistency with Dragoman 2018.

** Harada 2008 and Harada 2017 are incorporated into the summary for Brown 2018.

†† Backman 2005 and Dinger 2011 are incorporated into the summary for Samson 2016.

Results – Synthesis Details

FAQ 1: What does the treatment involve?

On preparing this FAQ, we felt the scoped elements would possibly be better addressed as three distinct "sub-FAQs" for the hormonal options, namely:

(1) How will I take this treatment?,
(2) Will it change my menstrual period?, and
(3) Will it change my ability to get pregnant?

Accordingly, we adopted these headings below for all the hormonal options.

Regarding impact on fertility, all the hormonal therapies below belong to classes of medicines that are also used to impede or essentially prevent pregnancy during their use (i.e., they have contraceptive effects). However, when used in endometriosis, this is not their goal; some women may find their contraceptive effects desirable, while other women may find them distressing. The hormonal options in this evidence report are not considered to have permanent contraceptive effects, but the rapidity with which a woman might be able to conceive after deciding to discontinue one of the hormonal therapies may vary. For instance, once a woman stops taking a progestin-only pill, she will usually have rapid return of menstruation/fertility, but if a woman who recently received a progestin depot injection decides she wants to get pregnant, she will need to wait for at least as long as the duration of the injection's activity (about 12 weeks) and possibly longer (discussed further below). In general, if a woman desires to get pregnant, the hormone-based therapies for endometriosis are only a temporizing measure (i.e., they are not considered a viable long-term option); many of these women may want to consider surgical approaches to endometriosis instead.

Because of the common sources used for these descriptive responses, we provide one collective citation at the end of this FAQ.

Medical treatments for endometriosis aim to reduce symptoms related to endometriosis, such as pain. These treatments can be used instead of or in addition to surgical treatment; when used in addition to surgical treatment, the medication is often used with the hope of preventing recurrence. With specific regard to the progestin-releasing intrauterine device, this is often used preceding or following surgery.

Some women may also want to use non-pharmacologic and non-surgical approaches to help with their pain, such as exercise and relaxation techniques.

Symptomatic treatment alone (no hormonal therapy)

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Symptomatic therapy involves treating the symptoms of endometriosis without using any kind of hormone-based therapy. This could include different treatments, such as local application of heat, non-steroidal anti-inflammatory drugs (NSAIDs), or – in cases with moderate to severe pain – opioids (though opioids are used sparingly if possible and are often limited by their side effect profile). As stated in Scoping, we will focus here on NSAIDs.

NSAIDs include medicines like ibuprofen and naproxen, and they can be used as needed (naproxen has a longer duration of action than ibuprofen). There are also prescription NSAIDs, some of which only need to be taken once a day.

Descriptive Summary Results

You can use things like heat at painful areas. You can also take medicines that do not have hormones in them. This includes medicines like ibuprofen or naproxen. If the pain is very bad, you might try tramadol or opioids. However, tramadol and opioids are not used unless pain is not relieved enough with other treatments. Medications that do not have hormones in them can be used with medications that do have hormones in them.

Combined estrogen plus progestogen pill (combined oral contraceptives)

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

This intervention is often called “combination oral contraception” or “combined oral contraceptives” and abbreviated as COC or COCP (“P” in the latter for “pill”). Traditional use of COC involves taking 1 tablet every day for 3 weeks and then taking a break for a week (which may involve taking inert pills with or without iron). Alternatively, the patient may take a week-long break after 3 months of treatment (“tricycling”), or not take a break at all (“long cycle” or “continuous” therapy). Although existing evidence is specific to the cyclic use of the combined oral contraceptive pill, continuous use and tricycling are also commonly used in clinical practice and considered to be effective.

When taking COC, women will usually not have a menstrual period unless they are taking a week-long break/taking the inert pills. Women may also find that the menstrual periods they do have (if any) are lighter and shorter. However, some women may have spotting or metrorrhagia (irregular bleeding, especially between menstrual cycles, and sometimes even called intermenstrual bleeding), perhaps particularly in the initial months of use. A woman can stop taking COC at any time, and although COC has a contraceptive effect while being used, it is not considered to have any long-term effect on fertility. However, a small number of women may notice a delay between when they stop COC and when their menstruation/fertility returns.

Descriptive Summary Results

How will I take this treatment?

You will take 1 pill every day that has 2 hormones in it. Every month or every 3 months, you might have a week where you stop taking the pill with hormones in it. During this week, you might take a different pill or no pill at all. After that week, you will start taking the pill with hormones again. You can stop taking this medicine at any time.

Will it change my menstrual period?

When a woman is first using this medicine, she may have some spotting or bleeding at random times. This might last for a couple of months. If women have weeks where they stop taking the pill with hormones in it, they will usually have a menstrual period. But it may be shorter and lighter than usual.

Will it change my ability to get pregnant?

This kind of medicine is also used by women who do not want to get pregnant. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. These things will likely happen quickly if you stop using this medicine. However, for a small number of women, there might be a delay.

Progestogen pill

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The progestogen-only pill is sometimes colloquially referred to as the “mini pill”, and it is sometimes abbreviated POP. Using a POP involves taking 1 pill daily on a continuous basis (i.e., no break as is sometimes used with COC). Women may have spotting, perhaps particularly in the initial months of use. They may also have metrorrhagia, but the bleeding is often lighter than a typical menstrual period. Some women may have no bleeding. A woman can stop taking her POP at any time, and although POPs have a contraceptive effect while being used, they are not considered to have any long-term effect on fertility. Women will typically notice a rapid return of menstruation/fertility if they stop taking their POP. Dienogest is licensed specifically for endometriosis symptoms, and although it would be expected to have the same contraceptive effects as the POP class (and indeed, labeling information for dienogest discusses inhibition of ovulation and when a woman can generally expect her menstrual period to return after discontinuation), women are generally advised to use a nonhormonal method of contraception while on dienogest. Use of dienogest during pregnancy is contraindicated, so we do not include the caveat of “if a woman does not want to get pregnant” when discussing the advice to use a nonhormonal method of contraception while on dienogest.

Descriptive Summary Results

How will I take this treatment?

You will take 1 pill every day that has 1 hormone in it. You can stop using it at any time.

Will it change my menstrual period?

When a woman is using this medicine, she may have some spotting or bleeding at random times. This might happen most when she is first starting the medicine. If a woman has bleeding, it may be shorter and lighter than her normal menstrual period. Some women have no bleeding.

Will it change my ability to get pregnant?

This kind of medicine is also used by women who do not want to get pregnant. One of the progestogen pills is called dienogest, and it is not used to block pregnancy. Women taking dienogest should always use something that blocks pregnancy without hormones, like a condom. If you stop using this kind of medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. These things will likely happen quickly if you stop using this medicine.

Progestogen injection/depot

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The progestogen depot injection (medroxyprogesterone acetate) involves getting an injection every 3 months into the gluteal (buttock) or deltoid (shoulder) muscle. Women may initially have spotting, metrorrhagia, and/or prolonged bleeding. After 12 months of use, women typically find they have no menstrual periods at all. Once the injection has been given, it cannot be reversed or removed. Although progestogen depot injection has a contraceptive effect while being used, it is not considered to have any long-term effect on fertility. However, for some women, it can take up to a year for menstruation/fertility to return.

Descriptive Summary Results

How will I take this treatment?

You will get an injection of a hormone every 3 months. The injection will be in your shoulder or bottom. Once the injection has been given, it cannot be removed or reversed.

Will it change my menstrual period?

At first, women may have spotting, bleeding at random times, or bleeding that lasts longer than usual. However, after women have been using this medicine for about a year, most have no bleeding.

Will it change my ability to get pregnant?

This medicine is also used by women who do not want to get pregnant. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. However, this can take up to a year for some women.

Progestogen intrauterine system

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The progestogen intrauterine system (levonorgestrel intrauterine system) is very often abbreviated as IUD (intrauterine device) or IUS (intrauterine system). There are also non-hormonal IUDs (i.e., the copper IUD), but those are not considered in this evidence report, and any reference to an IUD should be understood to be a reference to a levonorgestrel IUD. Using an IUD involves having a qualified health care professional insert a small, "T"-shaped device into the uterus through the vagina and cervix. This does not take long to do and can be done in the office/outpatient setting. The IUD will need to be removed or replaced every 3 to 5 years depending on the type used. Women may have changes in their menstrual periods initially, which may lead to lighter or heavier menstrual bleeding. Sometimes, menstrual periods are more uncomfortable than they typically are. Women may also have some spotting or metrorrhagia. If these things occur, they usually subside within 3 to 6 months, and some women eventually stop having menstrual periods altogether. The IUD can be removed at any time, but just like with insertion, removal must also be done by a qualified health care professional. Although an IUD has a contraceptive effect while being used, it is not considered to have any long-term effect on fertility. Women typically have a rapid return of menstruation/fertility once they stop using the IUD.

Descriptive Summary Results

How will I take this treatment?

You will have a small device shaped like a "T" inserted into your uterus. This can be done in the office and does not take long. The device slowly releases a hormone and lasts for 3 to 5 years. You can have it removed at any time, but it must be done by a health care professional.

Will it change my menstrual period?

At first, women may notice they have more pain and lighter or heavier bleeding with their menstrual period. Some women may have spotting or bleeding at random times. If these things happen, they usually get better within 3 to 6 months. Some women stop having any menstrual bleeding.

Will it change my ability to get pregnant?

This medicine is also used by women who do not want to get pregnant. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. These things will likely happen quickly if you stop using this medicine.

Progestogen implant/subcutaneous

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

The subcutaneous progestogen implant involves a qualified health care professional placing a small rod (about the size of matchstick) under the skin on the inside part of the upper arm. This does not take long to do and can be done in the office/outpatient setting. The implant contains either etonogestrel or levonorgestrel. It will need to be removed or replaced every 3 years. Women may have lighter or heavier periods or spotting and metrorrhagia. Some women have no periods at all. Whatever a woman experiences in the first 3 months while using the subcutaneous progestogen implant is likely to be what she experiences for the rest of the time she uses the implant. The implant can be removed at any time, but like insertion, removal must be done by a qualified health care professional. Although the subcutaneous progestogen implant has a contraceptive effect while being used, it is not considered to have any long-term effect on fertility. Women typically have a rapid return of menstruation/fertility once they stop using the subcutaneous progestogen implant.

Descriptive Summary Results

How will I take this treatment?

You will have a rod about the size of a matchstick inserted under the skin of your inner arm. This can be done in the office and does not take long. The rod slowly releases a hormone and lasts for 3 years. You can have it removed at any time, but it must be done by a health care professional.

Will it change my menstrual period?

Women may have lighter or heavier bleeding with their menstrual period, or they may stop having menstrual periods. Some women may have spotting or bleeding at random times. Whatever happens during the first 3 months of use often continues for the rest of the time a woman uses this medicine.

Will it change my ability to get pregnant?

This medicine is also used by women who do not want to get pregnant. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. These things will likely happen quickly if you stop using this medicine.

Gonadotropin releasing hormone analogue/agonist injection/depot

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Despite their name, continuous administration (about 2 weeks or more) of gonadotropin releasing hormone (GnRH) agonists in women with endometriosis actually causes a hypoestrogenemic and hypoprogestinemic state (i.e., lowered levels of estrogen and progestin) due to downregulation of GnRH receptors and pituitary desensitization. Treatment with a GnRH agonist involves getting an injection or using a nasal spray. For this evidence report, however, we do not specifically consider nasal spray formulations. How often a woman will need to get an injection may vary, but it is common to get injections monthly or every three months depending on the medication and dose used. For instance, leuprolide may be given monthly at a lower dose or every three months at a higher dose, whereas goserelin is typically given monthly. Most women have no bleeding after using a GnRH agonist for 2 months. However, a woman may initially have up to 5 days of spotting or bleeding after using a GnRH agonist for about 2 weeks. GnRH agonists are not used for contraception, but a woman is unlikely to become pregnant while using a GnRH agonist. However, because GnRH agonists have a pronounced teratogenic profile, women should talk with their health care professional about any extra steps they might want to consider (such as using condoms) to ensure they do not become pregnant. GnRH agonists are not considered to have any long-term effect on fertility. However, return of menstruation/fertility can take up to 6 to 10 weeks after stopping the GnRH agonist.

Descriptive Summary Results

How will I take this treatment?
You will get an injection of a medication that acts like a hormone, and it is often given every month or every 3 months. Once you get the injection, it cannot be reversed or removed.

Will it change my menstrual period?
After the first two weeks, women may have spotting or bleeding for up to 5 days. Most women have no bleeding after 2 months.

Will it change my ability to get pregnant?
Women using this medicine are unlikely to get pregnant. However, if a woman gets pregnant while using this medicine, the medicine can hurt the baby. Because of this, your health care professional may suggest using extra methods to make sure you do not get pregnant while using this medicine. If you stop using this medicine, your chances of getting pregnant will go back to what they were before starting the medicine. Your menstrual period will also come back. However, this may take up to 6 to 10 weeks.

(HHS 2019, NICE 2017, Wood nd)

FAQ 2: Will my pain get better?

Effects of hormonal medical treatments vs. placebo/expectant management or another hormonal treatment

Evidence Review

Women with endometriosis often report pain as a key symptom – if not *the* key symptom. Commonly, this pain includes dysmenorrhea (painful menstruation) or cyclic pain in the abdomen and/or pelvis associated with a woman's menstrual period. Women can also experience dyspareunia (painful intercourse). In Scoping, we noted pain relief was the key outcome but that we would consider specific pain subscales such as dysmenorrhea or dyspareunia if there was sufficient evidence. While preparing this evidence report, it became evident that the pain outcomes most consistently reported were overall pain relief and relief from dysmenorrhea. Other pain-related outcomes were more sparsely and/or inconsistently reported, and some lacked a reasonable expectation for improvement with hormonal therapy (e.g., cyclic pain unrelated to the menstrual cycle). Accordingly, we focused on overall pain relief and dysmenorrhea for this FAQ.

Direct evidence comparing hormonal treatments to placebo or expectant management is limited. Across 4 systematic reviews (Brown 2018, Grandi 2019, Jensen 2018, and NICE 2017), there were a total of 6 distinct trials comparing a hormonal agent to placebo or expectant management: 2 comparing combination oral contraceptives vs. placebo (Harada 2008 and Harada 2017; total n = 327), 1 comparing an intramuscular GnRH agonist vs. placebo (Ling 1999, n = 88), and 3 comparing a levonorgestrel intrauterine system to expectant management (Vercellini 2003, n = 40; Tanmahasamut 2012, n = 55; Chen 2017, n = 80).

Direct comparative evidence for the effects of hormonal therapies on overall pain and/or dysmenorrhea

Source	No. studies (no. participants); Author year of studies	Treatment comparison	Outcome	Results	Certainty (reason for downgrade)
Brown 2018	1 (96); Harada 2008	combination oral contraceptive vs. placebo	dysmenorrhea (verbal rating scale, 0 to 3)	MD -1.30 (95% CI -1.84 to -0.76)	Moderate[1]
	2 (327); Harada 2008 & 2017	combination oral contraceptive vs. placebo	dysmenorrhea (visual analogue scale*)	MD -23.68 (-28.75 to -18.62)	Moderate[2]
Grandi 2019	1 (40); Vercellini 2003	levonorgestrel intrauterine system vs. expectant management	recurrence of moderate or severe dysmenorrhea	ARD -35% (95% CI -7.21% to -57%)	Moderate[3‡]
	1 (55); Tanmahasamut 2012	levonorgestrel intrauterine system vs. expectant management	dysmenorrhea (visual analogue scale†)	greater decrease in women receiving levonorgestrel intrauterine system	
	1 (80); Chen 2017	levonorgestrel intrauterine system vs. expectant management	dysmenorrhea pain (visual analogue scale†) and dysmenorrhea recurrence	greater decrease for both outcomes in women receiving levonorgestrel intrauterine system	
NICE 2017	1 (88); Ling 1999	leuprolide vs. placebo	dysmenorrhea (visual analogue scale, 0 to 10)	MD -6.30 (95% CI -9.93 to -2.67)	Low[1,4]

Jensen 2018 does not appear in this table because it did not have any additional placebo-controlled or expectant-management controlled trials compared with those in Brown 2018.
* Brown 2018 indicates the range for Harada 2017 is 0-100 and the range for Harada 2008 is unknown (ie, "No details relating to scale"). Full text review of Harada 2008 did not provide additional detail, but the results might suggest a 0-100 scale.
† Details of scale not provided
‡ Certainty rated for the overall body of evidence for levonorgestrel intrauterine system vs. expectant management rather than per trial
1 Imprecision (single, small trial)
2 Risk of bias, with Harada 2017 having incomplete outcome data and representing approximately 70% of the weighted analysis
3 Risk of bias for all included trials
4 Assessment of efficacy took place immediately after the treatment period (as opposed to after a longer period of follow-up, which might better establish durability of effects; NICE review authors also downgraded for this reason)

Additionally, as noted in the introduction to this FAQ, the Jensen 2018 and Grandi 2019 systematic reviews both concluded evidence is insufficient to establish superiority of any given hormonal treatment compared to another, and the Brown 2018 systematic review only had 1 included small trial with data suitable for quantitative analysis (finding no clear difference between groups).

The 2017 NICE systematic review also provided a network meta-analysis to permit comparisons to placebo and across the many different treatment options in the absence of direct evidence for many of the options. However, although this is a key advantage of network meta-analysis in general, we have concerns about the degree to which indirectness factors into the quantified estimates, and we also have other concerns about the NICE review (mainly related to risk of bias) that ultimately lead us to have Very low certainty in the quantified network estimates (see Critical Appraisal for details). Reassuringly, however, among the other systematic reviews, Grandi 2019 and Jensen 2018 both explicitly concluded that evidence was insufficient to establish superiority of any particular hormonal treatment, and this is consistent with the qualitative conclusions one can reach from the NICE review's quantified estimates. In the Brown 2018 systematic review, only 1 small trial (Vercellini 1993; n = 50) comparing 2 active treatments (combination oral contraceptive vs. goserelin) met inclusion criteria and provided data suitable for quantitative analysis (2 other trials met Brown 2018's inclusion criteria but did not provide data suitable for analysis). This trial found no clear difference between the treatments at the 6-month follow-up point following 6 months of treatment.

Pairwise and network meta-analytic results for hormone therapies on pain relief measured on a 0 to 100 visual analogue scale (NICE 2017)

The table below summarizes the results of the NICE 2017 pairwise and multivariate network meta-analysis. Results are reported as mean differences between the column-defined and row-defined treatments. The upper right section of the table presents results of pairwise meta-analyses (when available) and the lower left section of the table presents results from the multivariate network meta-analysis. Numbers in bold are reported for results that show significant difference between interventions.

placebo/no treatment	**-12.3 (95% CI -12.7 to -11.9)**				**-18.6 (95% CI -20.4 to -16.8)**
-12.6 (95% CrI -15.3 to -9.8)	***progestogen (oral)***			**1.5 (95% CI 0.7 to 2.3)**	
-13.2 (95% CrI -16.2 to -10.1)	-0.6 (95% CrI -1.8 to 0.6)	***progestogen (i.m.)***			
-17.7 (95% CrI -25.5 to -9.8)	-5.1 (95% CrI -12.8 to 2.7)	-4.5 (95% CrI -12.4 to 3.4)	***progestogen (i.u.)***	-1.4 (95% CI -2.8 to 0.1)	
-15.7 (95% CrI -21.3 to -10.1)	-3.2 (95% CrI -8.5 to 2.2)	-2.6 (95% CrI -8.1 to 2.9)	1.9 (95% CrI -3.4 to 7.3)	***GnRHa (i.m.)***	
-15.1 (95% CrI -20.8 to -9.3)	-2.5 (95% CrI -8.0 to 3.0)	-1.9 (95% CrI -7.6 to 3.7)	2.5 (95% CrI -2.8 to 8.1)	0.7 (95% CrI -0.2 to 1.5)	***progestogen (oral) plus estrogen (oral)***

i.m. = intramuscular; i.u. = intrauterine

The multivariate network meta-analysis incorporated additional information that permitted establishment of a common scale (visual analogue scale from 0 to 100) for all treatments, even if the contributing evidence was originally measured on a different scale (eg, progestogens i.m., GnRHa i.m., and progestogen oral plus estrogen oral). The NICE review authors did not include pairwise results involving these treatments in this table because they would be reported on different scales. They also noted that multivariable and univariable network meta-analysis results were broadly similar when available for comparisons. The NICE review authors also reported a network meta-analysis for a subset of trials that reported on pain relief specific to dysmenorrhea which included only 1 comparison relevant to our scoped outcome (ie, GnRHa i.m. vs. placebo) and found a significant benefit of GnRHa i.m. vs. placebo on pain relief specific to dysmenorrhea, consistent with the finding of GnRHa i.m. vs. placebo on the 0 to 100 visual analogue scale.

We rated the certainty of these findings as Very low due to indirectness and risk of bias (further details are in Critical Appraisal).

Evidence Synthesis

Outcome	Approach taken and justification	Results
pain	**Multiple systematic reviews already done, qualitative expression** Across 4 systematic reviews (Brown 2018, Grandi 2019, Jensen 2018, and NICE 2017), there were 6 distinct trials comparing a hormonal treatment to placebo or expectant management (Chen 2017, Harada 2008, Harada 2017, Ling 1999, Tanmahasamut 2012, Vercellini 2003). One systematic review (NICE 2017) provided a network meta-analysis to permit inference for options where placebo-controlled or expectant management-controlled trials were lacking; it also permits comparisons across the various treatment options even in the absence of direct comparisons. Qualitative expression was selected because providing numerical estimates for continuous outcomes may be difficult to understand or possibly even misleading. Although some treatments have findings with dichotomous outcomes (e.g., levonorgestrel intrauterine system, with Vercellini 2003 reporting absolute risk differences in recurrence of dysmenorrhea), preferentially highlighting or reporting on these outcomes would be inappropriate, as it would constitute a form of selective reporting bias. Finally, in many instances, we had serious concerns about the certainty of the underlying evidence. Therefore, we adopted a qualitative framework for all the options. For the direct evidence noted above, trials reported on dysmenorrhea. For the multivariate network meta-analysis, the NICE 2017 authors transformed various scales to an overall visual analogue pain scale from 0 to 100. To provide coherent and consistent synthesis, we consider it reasonable to conclude that each of the various treatments reduce pain overall, but that the greatest benefit in pain may be from pain related to a woman's menstrual period. This is supported by both the direct evidence and by the pathophysiology of endometriosis (i.e., where the greatest benefit would be expected). Although there are treatments for which direct evidence for impact on dysmenorrhea may be lacking, we consider it exceptionally unlikely that the treatment would reduce an overall pain measure but not a pain measure more specific to the condition for which it is being used.	**Moderate certainty of improvement in pain for combination oral contraceptives vs. placebo** **Moderate certainty of improvement in pain for levonorgestrel intrauterine system vs. expectant management** **Low certainty of improvement in pain for intramuscular gonadotropin-releasing hormone vs. placebo** **Very low certainty of improvement in pain for other treatments (progestogen-only pill, depot progestogen, and implant progestogen) vs. placebo or expectant management** **Very low certainty of no important difference in pain reduction between hormonal treatment options**

Descriptive Summary and Evidence Synthesis Results

Women who treat their symptoms without hormones may notice their pain get better, get worse, or stay about the same. This depends on the treatments a woman uses. Options include heating pads or medication like ibuprofen or naproxen. If the pain is really bad, tramadol or opioids might be used, but they are used for as short a time as possible. (Certainty rating not applicable)

Women who take a combination oral contraceptive may have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Moderate certainty based on 2 systematic reviews [Brown 2018, NICE 2017])

Women who take a progestogen-only oral contraceptive might have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Very low certainty based on 1 systematic review [NICE 2017])

Women who use a progestogen injection might have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Very low certainty based on 1 systematic review [NICE 2017])

Women who use a progestogen intrauterine system may have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Moderate certainty based on 2 systematic reviews [Grandi 2019, NICE 2017])

Women who use a progestogen implant might have more improvement in their pain compared to treating symptoms without hormones. (Very low certainty based on 1 systematic review [NICE 2017])

Women who use an injection of a gonadotropin-releasing hormone agonist might have more improvement in their pain compared to treating symptoms without hormones. The treatment may work best for pain related to your menstrual period. (Low certainty based on 1 systematic review [NICE 2017])

The different hormone treatments might all decrease pain by a similar amount. (Very low certainty based on 1 systematic review [NICE 2017])

FAQ 3: Will my quality of life get better?

Effects of hormonal medical treatments vs. placebo/expectant management or another hormonal treatment

Evidence Review

Of the 4 systematic reviews investigating efficacy (Brown 2018, Grandi 2019, Jensen 2018, and NICE 2017), Brown 2018 did not report on quality of life.

The NICE 2017 review identified only 1 relevant RCT (Petta 2005, n = 83, but only 68 providing data for analysis), which compared leuprolide vs. levonorgestrel intrauterine system. Although it found no clear difference between the two treatments, we consider this single small trial to be insufficient evidence to draw conclusions about this comparison.

Jensen 2018 included 3 RCTs that measured quality of life (all using the SF-12 or SF-36, which are on a 0 to 100 scale): Di Francesco 2014 (n = 30, COCP vs. leuprolide), Vercellini 2002 (n = 90, COCP vs. oral cyproterone), and Zupi 2004 (n = 133, COCP vs. leuprolide vs. leuprolide + transdermal ethinyl estradiol and oral norethindrone). The authors conclude "Taken together, the findings from the RCTs support that QoL [quality of life] is improved with cyclic combined OC [oral contraceptives], continuous combined OC, GnRH agonist, and oral progestin treatment", but without any "consistent significant differences" between treatments. They considered the quality of evidence as low, and we would downgrade the certainty of their statement to Very low, as the measurements of quality of life were changes from baseline (rather than a between-group difference at a certain time and without placebo control or expectant management control), there was inconsistency in the results (e.g., Zupi 2004 did not show significant change from baseline for combined oral contraceptives or leuprolide; only the group receiving leuprolide + transdermal ethinyl estradiol and oral norethindrone showed significant improvement from baseline for some domains but not others), and the improvements from baseline were in some cases statistically significant but of clinically-questionable relevance (e.g., Di Francesco 2014 is noted as showing a change from 39.5 to 46 and 46.9 to 49 for COCP and GnRH agonist, respectively; these are both considered statistically significant, but the clinical relevance of a 6.5-point and 2.1-point difference out of 100 is very questionable).

Grandi 2019 also concludes that combined oral contraceptives and progestin-only treatments lead to "improvement from baseline in QoL [quality of life]". However, we consider the following to be important limitations to such a claim (example citations given where relevant, though they are not necessarily an exhaustive list):

- their claim concerns improvements from baseline (rather than between-group differences at a set time)
- many are observational studies (Scala 2018, Morotti 2014, Grandi 2015)
- there is concerningly-discrepant information about the number of trials included in their review (e.g., compare Tables 1 and 2 to their "Limitations" section)
- not reporting on quality of life at all (Vercellini 2008)
- only reporting on an outcome for which "quality of life" would arguably be an inappropriately broad application of the construct (Muzii 2011, where the closest outcome we found was a categorical rating of treatment satisfaction)

In the one placebo-controlled or expectant management-controlled trial reporting on quality of life included in Grandi 2019 (Tanmahasamut 2012, n = 55), Grandi 2019 notes quality of life (as assessed by SF-36) "improved" in women receiving a levonorgestrel intrauterine system but "did not change" among those in the expectant management group. However, it only measured change in SF-36 from baseline (rather than a difference between the groups at a defined time point) and no quantified estimates or inferential statistics are given.

Evidence Synthesis

Outcome	Approach taken and justification	Results
quality of life	**Preponderance of evidence, qualitative expression** Across 3 systematic reviews reporting on quality of life (Grandi 2019, Jensen 2018, NICE 2017), evidence on quality of life is: relatively sparse (especially placebo-controlled or expectant management-controlled evidence), often measured as a change from baseline rather than between groups, and at times inconsistent or of questionable clinical relevance. Taken together and considering also the results for pain (FAQ2), we think it is reasonable to conclude with Very low certainty that quality of life may improve to a certain degree compared to what it was prior to starting hormonal therapy while emphasizing both our uncertainty and that quality of life may not change or may not change enough to be a noticeable difference. We note that certain options have no evidence (namely, depot progestogen and implant progestogen), but given the extent to which we are stating our uncertainty, we think it is reasonable to adopt the same general conclusion for these therapies as well. It does not seem there is a compelling prior probability of a substantive difference in efficacy between the hormonal treatments. However, side effects and medication burden can also impact quality of life.	**Very low certainty of a possible improvement in quality of life, but with uncertain magnitude and comparisons**

Descriptive Summary and Evidence Synthesis Results

Women who treat their symptoms without hormones may notice their quality of life get better, get worse, or stay about the same. This depends on the treatments a woman uses. Options include heating pads or medication like ibuprofen or naproxen. If the pain is really bad, tramadol or opioids might be used, but they are used for as short a time as possible. (Certainty rating not applicable)

Women using a hormone treatment may have an improvement in their quality of life compared to what it was before treatment. However, some women may not have any noticeable improvement. (Very low certainty based on 3 systematic reviews [Grandi 2019, Jensen 2018, NICE 2017]) **Symptom treatment without hormones may also improve a woman's quality of life.** (Certainty rating not applicable) **We do not have enough research to know how treatments compare to each other.** (Insufficient evidence based on 3 systematic reviews [Grandi 2019, Jensen 2018, NICE 2017])

FAQ 4: What are the side effects or risks?

We pre-specified that we would conduct an evidence review on three specific risks: discontinuation of treatment due to adverse events, venous thromboembolism, and breast cancer. Each of the three risks is summarized separately below.

Withdrawals due to adverse events

Effects of hormonal medical treatments vs. placebo/no treatment or another hormonal treatment

Evidence Review Table

The NICE 2017 systematic review provides quantified estimates for withdrawals due to adverse effects for various hormone therapies for endometriosis. These quantified estimates are presented as ORs without accompany baseline risks, which impedes translation into an absolute estimate (with absolute estimates being far more meaningful for patients and clinicians than a relative effect estimate in isolation). Additionally, given the Very low certainty in these estimates (risk of bias, inconsistency, indirectness, and imprecision) and our concerns about the plausibility of certain estimates, we do not think it is appropriate to provide quantified or comparative estimates of effect. For instance, for the network estimate for the comparison of progestogen pill vs. placebo/expectant management, the reported OR is 17.9 (95% CrI 1.76 to 676); for intramuscular gonadotropin-releasing hormone agonists vs. placebo, it is 17.4 (95% CrI 1.66 to 701); for subcutaneous gonadotropin-releasing hormone agonists vs. placebo, it is 5.4 (95% CrI 0.34 to 251), and for combination oral contraceptives, it is 0.48 (95% CrI 0.04 to 5.53). Thus, even if these estimates had been accompanied by baseline risks, the extremely wide CrIs would still impede any kind of meaningful quantitative inference about this outcome (further details are in Critical Appraisal). Instead, we provide descriptive responses of adverse events that may be experienced with the various options, with the obvious clinical reality that some women may find the adverse effects intolerable enough that they decide to discontinue treatment.

Evidence Synthesis Process

Outcome	Approach taken and justification	Results
discontinuation due to adverse events	**Descriptive summary** Due to concerns we have about the certainty and plausibility of the quantified estimates, we do not think it is appropriate to provide quantitative or comparative synthesis statements. Therefore, we provide a descriptive summary of adverse events.	**Not applicable** See below for a summary of common adverse events with each of the options considered in this evidence report. The serious adverse events we scoped (venous thrombotic events and breast cancer) are addressed separately.

Option-specific adverse events

Because of the common sources used for these descriptive responses, we provide one collective citation at the end of this section. The various progestogen-based options do not have the same responses for some of the adverse events. Although the administration method is not likely a factor for most options (with the levonorgestrel intrauterine system being a possible exception due to its effects being primarily local, with considerably lower systemic absorption), there are different progestogens used for different administration methods and we are unable to determine if the differences are due to the specific medications or other factors that may influence how sources report adverse effects.

Symptomatic treatment alone (no hormonal therapy)

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with non-hormonal treatments depend on the treatment being used. Using topical heat does not usually have side effects. Non-steroidal anti-inflammatory drugs like ibuprofen and naproxen can cause upset stomach and heart burn. Tramadol and opioids can cause fatigue, dizziness, constipation, and upset stomach; they can also be addictive.

Descriptive Summary Results

Side effects depend on what kind of symptomatic treatment you use.

- **Using heat at painful areas does not usually have any side effects.**
- **Medications like ibuprofen and naproxen can cause upset stomach and heart burn.**
- **Tramadol and opioids can be addictive, and they can also cause fatigue, dizziness, constipation, upset stomach.**

Combined estrogen plus progestogen pill

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with combination estrogen and progestogen pills may include headache, increased appetite, weight gain, nausea, fluid retention, bloating, breast tenderness, and mood changes. Depending on the specific medicine used, women may notice new or worsening acne, or they may notice their acne gets better. Sometimes women having certain side effects on one kind of combination do not have side effects or have fewer or different side effects when trying a different combination.

Descriptive Summary Results

Side effects may include:

- **headache**
- **feeling hungry more often**
- **weight gain**
- **nausea**
- **fluid buildup and bloating**
- **mood changes**
- **your breasts feeling tender**

Depending on the specific medicine used, women may notice new or worsening acne, or they may notice their acne gets better.

If you have side effects that bother you, trying a different type of pill may help decrease side effects or make them more tolerable.

Progestogen pill

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with progestogen-only pills include may include headache, increased appetite, weight gain, nausea, fluid retention, bloating, breast tenderness, and mood changes. Depending on the specific medicine used, women may notice new or worsening acne, or they may notice their acne gets better. Sometimes women having certain side effects on one type of progestogen do not have those side effects or have fewer or different side effects when they try a different progestogen.

Descriptive Summary Results

Side effects may include:

- **headache**
- **feeling hungry more often**
- **nausea**
- **fluid buildup and bloating**
- **mood changes**
- **your breasts feeling tender**

Depending on the specific medicine used, women may notice new or worsening acne, or they may notice their acne gets better.

If women take dienogest, they may also notice symptoms like hot flashes and weight gain. This may be due to how dienogest works.

If you have side effects that bother you, trying a different type of pill may help decrease side effects or make them more tolerable.

Progestogen injection/depot

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with depot progestogen injection may include acne, hair loss, fatigue, dizziness, abdominal discomfort, headache, weight gain, and mood changes. With long-term use, some women may have decreased bone mineral density, but if this occurs, normal bone health typically returns if this medication is discontinued.

Descriptive Summary Results

Side effects may include:

- **acne**
- **hair loss**
- **feeling tired or dizzy**
- **stomach pain**
- **headache**
- **weight gain**
- **mood changes**

When this medication is used for long periods of time, some women's bones may get thinner. If this happens, the bones can usually go back to normal health when a woman stops using this medication.

Progestogen intrauterine system

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with progestogen intrauterine system may include acne, abdominal discomfort, nausea, headache, and breast tenderness. Some women develop ovarian cysts, which can be painful but usually resolve without treatment beyond symptomatic therapy as needed.

Descriptive Summary Results

Side effects may include:

- **acne**
- **stomach pain**
- **nausea**
- **headache**
- **your breasts feeling tender**

Some woman get collections of fluid on their ovaries while taking this medication. These are called ovarian cysts. If this happens, the most common symptom is pain in your lower stomach or pelvis. The cysts usually go away without specific treatment.

Progestogen implant/subcutaneous

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with progestogen implants may include acne, abdominal discomfort, nausea, headache, weight gain, breast tenderness, and mood changes.

Descriptive Summary Results

Side effects may include:

- **acne**
- **stomach pain**
- **nausea**
- **headache**
- **weight gain**
- **mood changes**
- **your breasts feeling tender**

Gonadotropin releasing hormone analogue/agonist injection/depot

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

Side effects with gonadotropin releasing hormone agonists include menopause-like symptoms, like hot flushes and night sweats. Other common side effects may include nausea and vomiting, fluid retention, decrease in breast size, headaches, vaginal dryness/vaginitis, decreased libido, difficulty sleeping, acne, muscle pain, dizziness, and mood changes.

Descriptive Summary Results

Many of the side effects are like what a woman might feel when she is going through menopause.

Side effects may include:

- **hot flushes and night sweats**
- **vaginal dryness or irritation**
- **your breasts getting smaller**
- **difficulty sleeping**
- **mood changes**
- **less interest in sex**
- **acne**
- **muscle pain**
- **dizziness**
- **nausea and vomiting**
- **headaches**
- **fluid buildup**

(DynaMed 2018/2019, HHS 2019, NICE 2017, Wood nd)

Venous thromboembolism

A venous thromboembolism (VTE) is a blood clot that takes two primary forms:

- a deep venous thrombosis (DVT), which most commonly occurs in the deep veins of the leg (but much less commonly can occur in the deep veins of the arm), or
- a pulmonary embolism (PE).

A stationary blood clot at the site where it originated (i.e., an *in-situ* blood clot) is called a thrombus (the state of having one or more thrombi is called thrombosis). When a blood clot (or part of a blood clot) breaks off, moves to another area, and obstructs it, this is called thromboembolism. Some people may shorten this to "embolism", but there are other things that can embolize, such as fat and air. Although not all DVTs embolize, the feared consequence of a DVT embolizing is that it will progress to the pulmonary vasculature and cause a PE. DVTs and PEs both range in severity. Both are serious conditions that require urgent / emergent medical attention. They can range from causing relatively minor symptoms (e.g., swollen and painful leg in DVT, shortness of breath and rapid heart rate and breathing in PE) to being extremely dangerous or life-threatening (e.g., phlegmasia alba, phlegmasia cerulea dolens, saddle embolism). Accordingly, women and their clinicians should consider risk factors for venous thromboembolism (e.g., age, personal or family history) when considering which of the hormone-based treatments for endometriosis might be best.

Combined estrogen plus progestogen pill (combined oral contraceptives)

Evidence Review

The risk of a VTE while taking a combination oral contraceptive may vary depending on the progestogen used. This is demonstrated in both the systematic reviews examining this question (Dragoman 2018 and Oedingen 2018).

Summary of meta-analyses of observational studies on risk of VTE among users of combined oral contraceptives by progestogen type compared with levonorgestrel as the progestogen type (Dragoman 2018*)

Analysis	Cyproterone acetate			Desogestrel			Dienogest			Drospirenone			Gestodene			Norgestimate		
	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)
overall	n=9	39.9	**2.04 (1.55 to 2.49)**	n= 16	30.1	**1.83 (1.55 to 2.13)**	n=2	52.6	1.46 (0.57 to 5.41)	n=10	66.4	**1.58 (1.12 to 2.14)**	n=12	46.5	**1.67 (1.32 to 2.10)**	n=9	15.1	1.14 (0.94 to 1.32)
exclusion of poor-quality studies	n=8	43.1	**2.05 (1.59 to 2.53)**	n=14	29.7	**1.80 (1.51 to 2.08)**	n=1	NA	1.10 (0.54 to 2.25)	n=9	70.1	**1.58 (1.10 to 2.18)**	n=11	46.7	**1.63 (1.28 to 2.04)**	n=8	12.0	1.13 (0.91 to 1.31)

Bolding indicates statistically significant results. Results were generally consistent across multiple subgroup analyses.

* We identified an additional 2018 systematic review (Oedingen 2018) which reported consistent results of significantly increased overall risk of VTE for drospirenone, desogestrel, gestodene and cyproterone as progestogen type compared with levonorgestrel. In addition, Dragoman 2018 included a table that summarized four previously published meta-analyses that also found consistent results.

Certainty is Very low for dienogest (risk of bias and imprecision) and Low for the remaining progestogens (risk of bias).

Dragoman 2018 provides relative effect estimates with a levonorgestrel-containing combination oral contraceptive (LNGCOC) as the reference. We consider this reasonable given the concern of increased thrombogenic potential with later-generation progestogens in combined oral contraceptives. However, to make results meaningful for patients, absolute risks are needed (and these are not obtainable from Dragoman 2018). Specifically, one needs an absolute risk among women using LNGCOC, from which one can estimate absolute risks if using any of the above progestogens. Such an estimate is available from the large and representative cohort study Lidegaard 2009 (summarized in Critical Appraisal and leading to an estimate of 0.55% over 10 years for women taking LNGCOC). Additionally, although the risk of venous thromboembolism among women not using any hormonal treatment may be very low, it would not be strictly correct to assume it is 0. Therefore, to provide a comparative framework for how combination oral contraceptives (or any other hormonal therapy) might increase the risk of venous thromboembolism, one needs an estimate of risk among people not using hormonal treatment. Lidegaard 2009 again provides such an estimate: 0.30% over 10 years.

Evidence Synthesis

Outcome	Approach taken and justification	Results
VTE	**Meta-analysis already done** Dragoman 2018 provides data for relative risk (RR) of various progestogen types as part of a combination oral contraceptive using a levonorgestrel-containing combination oral contraceptive (LNGCOC) as the reference. As noted above, although Dragoman 2018 provides RR estimates, to make the results more meaningful for an individual patient, one needs absolute risks. Given Dragoman 2018 used LNGCOC as the reference, one needs a baseline absolute risk of VTE for women taking LNGCOC. This baseline absolute risk can obviously inform the absolute risk for LNGCOC. However, it can also be used to estimate the absolute risks for other progestogen-containing combination oral contraceptives by using the absolute risk for LNGCOC as the baseline risk and then multiplying it by the RR data provided by Dragoman 2018. One would also ideally have an estimate of the risk of VTE among women who do not use any hormonal treatment (to permit inference about how different the risk is if using a combination oral contraceptive or any other kind of hormonal therapy). Based on the large and representative cohort study Lidegaard 2009, we estimate the risk of VTE as 0.55% over 10 years for women taking LNGCOC. Comparably, we estimate a 0.30% risk over 10 years among women not using any hormonal treatment (and we set this risk as the risk for the option of symptomatic treatment without hormonal therapy). Although certainty ratings were not carried out for these univariate estimates in Critical Appraisal, and although Lidegaard 2009 is likely a high-quality study in terms of any univariate estimate, we acknowledge that these univariate estimates are being explicitly used to inform comparative estimates/inferences. Accordingly, we assign a certainty of Low for evidence synthesis statements for coherence/consistency in reporting. Among the 4 progestogen types with significantly increased risk compared with LNGCOC (cyproterone acetate, desogestrel, drospirenone, and gestodene), although there are minor difference in point estimates, the CIs widely overlapped and there was little evidence of a substantive difference in risk among them. Therefore, we report the risk for these 4 progestogens as a range with the lower and upper bounds of the range being the highest (2.05; cyproterone acetate) and lowest (1.58;	**The risk of VTE among women using symptomatic treatment without hormones may be 0.30% over 10 years.** (Low certainty) **The risk of venous thromboembolic events may be 0.55% to 1.13% over 10 years when taking a combination oral contraceptive depending on the type of oral contraceptive used.** (Low certainty) The risk of venous thromboembolic events when taking a combination oral contraceptive may depend on the type of progestogen used. (Low certainty) • This risk may be 0.55% over 10 years for combination oral contraceptives where the progestogen is levonorgestrel (Low certainty), norgestimate (Low certainty), or dienogest (Very low certainty) • This risk may be 0.87% to 1.13% over 10 years for combination oral contraceptives where the progestogen is cyproterone, drospirenone, gestodene, or desogestrel. (Low certainty)

Outcome	Approach taken and justification	Results
	drospirenone) RR point estimates. This gives a lower-bound of 0.55% * 1.58 = 0.87% and an upper-bound of 0.55% * 2.05 = 1.13%. The progestogen norgestimate may not have an important difference in thromboembolic risk compared to LNGCOC (RR 1.14 [95% CI 0.94 to 1.32] or RR 1.13 [95% CI 0.91 to 1.31] depending on whether one excludes poor-quality studies). In the context of the very low baseline risk with LNGCOC (0.55% over 10 years), even the upper bound of the CI only translates to a 10-year risk of 0.73% (absolute difference of 0.18% over 10 years). Accordingly, for evidence synthesis statements, we set the risk for norgestimate as equal to LNGCOC. The same is possibly true for dienogest as well, though the CI bounds are considerably broader (RR 1.10 [95% CI 0.54 to 2.25] for the estimate excluding poor-quality studies). Although ideally we would have more evidence (and thus greater precision), we consider it reasonable to set the risk for dienogest as equal to the risk for LNGCOC with Very low certainty. Considering all the above, along with the fact that: (1) the evidence for these risks is observational in nature and of Low or Very low certainty, (2) the scope of this evidence report is not to differentiate among different combined oral contraceptives, but rather, to evaluate combined oral contraceptives as a class, and (3) the risk is fairly small regardless of the specific combination oral contraceptive being considered, we provide the risks separately (0.55% for levonorgestrel, norgestimate, and dienogest; 0.87% to 1.13% for cyproterone, desogestrel, drospirenone, and gestodene) and as an overall range from 0.55% to 1.13%, but we emphasize the overall range (assigning it Low certainty).	

Evidence Synthesis Results

Of 1,000 women who treat their symptoms without hormones, about 3 (0.3%) may get a blood clot over the next 10 years. (Low certainty based on 1 cohort study [Lidegaard 2009])

Of 1,000 women who take a combined oral contraceptive pill, about 5 to 11 (0.5% to 1.1%) may get a blood clot over the next 10 years depending on the type of combined oral contraceptive a woman uses. (Low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review and meta-analysis of observational studies [Dragoman 2018])

Progestogen-only products

Evidence Review

There were 2 systematic reviews in our search that reported on risk of VTE among women using progestogen-only contraceptives: Bergendal 2009 and Tepper 2016. All studies in Bergendal 2009 were also included in the more current Tepper 2016; as such, we did not critically appraise Bergendal 2009 in full and only mention it to note it is functionally supplanted by the more current Tepper 2016. No pooled estimates were reported for the progestogen-only products, all comparisons were vs. no hormonal therapy, and because Tepper 2016 served as the source for all progestogen-only compounds, we present this section as "Progestogen-only products" for efficiency and ease of comprehension.

Risk of venous thromboembolism (VTE) among women in general population using progestin-only contraceptives vs. nonusers, by type of progestin-only product (no pooled estimate reported for any of the following)

Agent	No. relevant analyses/studies	Key findings	Certainty (reason for downgrade)
depot medroxyprogesterone acetate (DMPA)	3	▪ two case-control studies found significantly increased odds of VTE among women using DMPA vs. nonusers ○ OR 3.0 (95% CI 1.2 to 7.5) in 1 study – diagnosed from "anticoagulation clinic" ○ OR 2.2 (95% CI 1.3 to 4.0) in 1 study – diagnosed from "medical records and imaging"; only included if started anticoagulation ▪ similar magnitude of risk that was not statistically significant (OR 2.2, 95% CI 0.7 to 7.3) in 1 case-control study – diagnosis verified by "medical records and imaging"	Very low certainty of increase in VTE with DMPA with downgrade for observational study design and additional downgrade for case-control study design (higher risk of bias)
implants	1	▪ 1 nationwide registry cohort study showed no significant difference in VTEs with use of implants in analysis limited to *confirmed* VTEs (rate ratio 1.4, 95% CI 0.6 to 3.4; these were the results reported in Fig 5 forest plot) but showed significant increase in analysis including *all* VTEs (rate ratio 2.1, 95% CI 1.3 to 3.5; these additional results reported in Results text) • 1 other study showed no significant difference in VTEs in population with use of implants and desogestrel POPs combined ○ Fig 5 forest plot indicated point estimate slightly	Very low certainty of increase in VTE with implant (based on assessment of implants only study, as noted above) with downgrades for observational study design and inconsistency (significant increase found only when outcome operationalized as all VTEs)

		favored decreased risk of VTE with intervention; effect estimate in Table 2 is OR 0.9 (95% CI 0.5 to 1.6) ○ because the population included both women with implants and women with desogestrel POPs, this study cannot directly address effects of implants specifically and is mentioned here only for completeness	
levonorgestrel-releasing intrauterine system	5	▪ none of 5 studies (including ≥ 1 nationwide registry cohort study) found increased odds of VTE among women using levonorgestrel-releasing intrauterine system vs. nonusers ○ point estimate favored decreased risk of VTE in all 5 studies, with OR ranging from 0.3 to 0.9 ○ highest upper bound of 95% CI was OR of 1.3 ○ includes relevant results from Lidegaard 2009 (summarized separately in this document)	Low certainty of no important increase in VTE with levonorgestrel-releasing intrauterine system with downgrade for observational study designs
progestin-only pills (POPs)	10 relevant analyses from 8 studies	▪ overall ○ no significant difference in 9 analyses/7 studies (including > 1 nationwide registry cohort study) of use of POPs for contraceptive purposes (point estimates of 4 favored increased risk and points estimates of 5 favored decreased risk, and with at least 2 included studies having non-overlapping CIs) ▪ includes relevant results from Lidegaard 2009 (Danish national registry based cohort study, summarized separately in this document) ○ significant increase (OR 5.9, 95% CI 1.2 to 30.1) in 1 analysis/study of women using POPs for therapeutic indications ▪ conditions being treated were not stated ▪ formulations and doses of POPs were not reported ▪ specific POPs evaluated - in addition to Lidegaard 2009 (included in Fig 5, but not included below because already summarized separately, and which reported Very low evidence of no important difference in venous thrombosis for women using the specific progestin-only oral pills levonorgestrel or norethisterone and desogestrel [with	*Overall* Very low certainty of no increase in VTE with POP with downgrades for observational study design and inconsistency *For specific POPs* Very low certainty of no important increase in VTE with POP with desogestrel with downgrades for observational study design and imprecision Very low certainty of no important increase in VTE with POP with norethisterone with downgrades for observational study design and imprecision

		non-users as reference standard] [with imprecision downgrade for both options]), one other study in Fig 5 (Lidegaard 2011 – also a Danish national registry based cohort study) also reported results separately for two specific progestogens included in POP as described below ○ no significant difference with POP with desogestrel with point estimate favoring decreased risk of VTE: 0.6 (95% CI 0.3 to 1.4) ○ no significant difference with POP with norethisterone with point estimate favoring decreased risk of VTE: 0.6 (95% CI 0.3 to 1.1)	

Evidence Synthesis

Each evidence synthesis below is based on the data provided by the systematic review Tepper 2016. The "approach taken" column discusses how we used the data in Tepper 2016 to provide synthesis statements.

Outcome (by progestin only product)	**Approach taken and justification**	**Results**
VTE with depot medroxyprogesterone acetate (DMPA)	**Range with upper and lower limits based on point estimates from studies showing lowest and highest increases** 3 case-control studies found increased odds of VTE in women using DMPA vs. nonusers and 2 were statistically significant. The 3 studies showed similar magnitudes of increase, with ORs of 2.2 in 2 studies and 3.0 in the third. We report the increase as a range with the bounds based on the lower and upper OR point estimates. As noted in the above section on combined oral contraceptives, we estimate a 0.30% risk of VTE over 10 years in women who do not use hormonal therapy. We used this baseline risk to estimate the absolute risk for DMPA. Because the baseline risk is so low, we consider it reasonable to treat the OR as functionally equivalent to the RR, and thus estimate 0.30% * 2.2 = 0.66% and 0.30% * 3.0 = 0.9%.	**The 10-year risk of VTE among women who use DMPA may be 0.66% to 0.9%** (Very low certainty)
VTE with implant	**Range with upper and lower limits based on 2 related point estimates from single study**	**The 10-year risk of VTE among women who use a progestogen**

Outcome (by progestin only product)	Approach taken and justification	Results
	1 nation-wide registry cohort study reported 2 relevant effect estimates: one from analyses limited to confirmed VTE (RtR 1.4, 95% CI 0.6 to 3.4); and another from analyses including all VTE (RtR 2.1, 95% CI 1.3 to 3.5). Although the increase was not significant in the analyses restricting to confirmed VTE, the 2 analyses showed consistent magnitudes of increase. We therefore report the increase as a range with the bounds based on the lower (confirmed VTE) and higher (all VTE) point estimates. As noted in the above section on combined oral contraceptives, we estimate a 0.30% risk of VTE over 10 years in women who do not use hormonal therapy. We used this baseline risk to estimate the absolute risk for progestogen implant. Thus, we estimate 0.30% * 1.4 = 0.42% and 0.30% * 2.1 = 0.63%.	**implant may be 0.42% to 0.63%** (Very low certainty)
VTE with levonorgestrel-releasing intrauterine system	**Set risk as equal to women who do not use hormonal therapy** None of 5 studies (including ≥ 1 nationwide registry cohort study) found increased odds of VTE among women using levonorgestrel-releasing intrauterine system vs. nonusers and point estimates favored decreased risk of VTE in all 5 studies (ORs ranged from 0.3 to 0.9). We consider it implausible that the levonorgestrel intrauterine system would actually decrease risk, so we instead conclude there may be no important increase. Because of this, we set the risk as 0.30% (as noted in the above section on combined oral contraceptives, we estimate a 0.30% risk of VTE over 10 years in women who do not use hormonal therapy).	**The 10-year risk of VTE among women who use a levonorgestrel intrauterine system may be 0.30%** (Low certainty)
VTE with progestin-only pills (POPs)	**Set risk as equal to women who do not use hormonal therapy** In 10 analyses from 8 studies, 9 showed no significant difference in VTE risk comparing women using POPs vs. non-users and 1 analysis/1 study showed significantly increased VTE risk among users. Among the 9 studies showing no significant differences between POP users vs. nonusers, point estimates favored increase in 4 and decrease in 5. There was statistical heterogeneity across analyses. 4 analyses/2 studies (both nationwide registry cohort studies) evaluated specific POPs (desogestrel in both studies and norethisterone and levonorgestrel or norethisterone in 1 study each) and all found no significant difference in VTE	**The 10-year risk of VTE among women who use a progestogen-only pill may be 0.30%** (Very low)

Outcome (by progestin only product)	Approach taken and justification	Results
	risk comparing users vs. non-users. In light of these results, we consider it reasonable to set the risk as equal to the risk among women who do not use hormonal therapy (as noted in the above section on combined oral contraceptives, we estimate a 0.30% risk of VTE over 10 years in women who do not use hormonal therapy).	

We also repeat the synthesis statement for women who do not use hormone-based treatment (described in more detail in the section on combination oral contraceptives) for reference.

Evidence Synthesis Results

Of 1,000 women:

- **who treat their symptoms without hormones, about 3 (0.3%) may get a blood clot over the next 10 years.** (Low certainty based on 1 cohort study [Lidegaard 2009])
- **about 3 (0.3%) may have a blood clot over the next 10 years if they use a progestogen-only pill.** (Very low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review [Tepper 2016])
- **about 7 to 9 (0.7% to 0.9%) may have a blood clot over the next 10 years if they use a progestogen injection.** (Very low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review [Tepper 2016])
- **about 3 (0.3%) may have a blood clot over the next 10 years if they use a progestogen intrauterine system.** (Very low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review [Tepper 2016])
- **about 4 to 6 (0.4% to 0.6%) may have a blood clot over the next 10 years if they use a progestogen implant.** (Very low certainty based on 1 cohort study [Lidegaard 2009] and 1 systematic review [Tepper 2016])

Gonadotropin releasing hormone analogue/agonist injection/depot

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

As noted in FAQ 1, despite their name, continuous use of a gonadotropin releasing hormone agonist actually results in a hypoestrogenemic and hypoprogestinemic state. Accordingly, there is little to no reason to think gonadotropin releasing hormone agonist would increase a woman's risk of a thromboembolic event. The lack of systematic reviews dedicated to this risk is therefore unsurprising, but we also conducted a search for original evidence reports, which yielded much the same, aside from 2 case reports purporting to attribute a thromboembolic event to the use of a gonadotropin releasing hormone agonist. Although we do not dismiss case reports as being entirely unhelpful, we do not consider case reports to have sufficient evidentiary strength to be included in evidence reports. We therefore conclude that use of a gonadotropin releasing hormone agonist may not increase a woman's risk of a thromboembolic event and set this risk as equal to 0.30%; as noted in the above section on combined oral contraceptives, we estimate a 0.30% risk of VTE over 10 years in women who do not use hormonal therapy. Because we gave this estimate a Low certainty rating, we apply the same certainty rating here given we are using this estimate for the option of gonadotropin releasing hormone agonist.

Descriptive Summary and Evidence Synthesis Results

Of 1,000 women who treat their symptoms without hormones, about 3 (0.3%) may get a blood clot over the next 10 years. (Low certainty based on 1 cohort study [Lidegaard 2009])

Of 1,000 women who use an injection of a gonadotropin-releasing hormone agonist, about 3 (0.3%) may get a blood clot over the next 10 years. (Low certainty based on 1 cohort study [Lidegaard 2009])

Breast cancer

Overview

Evidence Review

A single study was used as our only source for the effects of combined oral contraceptive pills (COCPs) and progestogen-only products on breast cancer risk (Mørch 2017).

For the effects of COCPs, we identified Mørch 2017 as the best source for COCP. As noted in Search and Selection and Critical Appraisal we also identified a well-known and highly-cited 1996 Lancet individual patient data meta-analysis (IPDMA), but we did not progress it beyond Search and Selection due to its very dated nature. Indeed, Mørch 2017 explicitly notes a motivating reason for their study was to provide contemporary data on breast cancer risk, and this is relevant in the context of different formulations for combination oral contraceptives (e.g., different estrogen doses) and different types of hormonal contraception (e.g., levonorgestrel intrauterine system) now being used/available. That said, the results from Mørch 2017 were largely consistent with those of the 1996 Lancet IPDMA for effects of COCP use on breast cancer risk (RR 1.24, 95% CI 1.15 to 1.33 in Lancet 1996 and RR 1.19, 95% CI 1.13 to 1.26 in Mørch 2017). Mørch 2017 also noted that, in line with their findings, previous studies have also not shown consistent differences in risk among combined oral contraceptives including different progestogen types. We note that explicitly given the apparent potential for a difference (albeit small) in the thrombogenic potential of the different progestogens used in combination oral contraceptives.

For the effects of different progestogen-only products, we identified a 2016 systematic review that evaluated progestin-only formulation exposure and breast cancer risk (Samson 2016). It included 6 studies evaluating different progestin-only formulations: 3 evaluated oral progestin [not further defined], 1 evaluated injections, 1 evaluated injections or implants, and 1 evaluated levonorgestrel-releasing intrauterine system. All 6 studies were graded Very low certainty, all were considered inferior in study design to the Mørch 2017 nationwide cohort study for the reasons described in Critical Appraisal (Samson 2016 summary, 'Other considerations'), and therefore, none were progressed to Evidence Synthesis.

We identified 2 additional studies evaluating progestin-only formulation exposure and breast cancer risk that appeared to meet Samson 2016 eligibility criteria but that were not among the 6 studies included in Samson 2016: Soini 2014 and Dinger 2011. Both studies evaluated a levonorgestrel intrauterine system. As further described in Critical Appraisal (Samson 2016 summary, 'Other considerations'), we identified design limitations in Dinger 2011 that led us to consider it much less reliable than Mørch 2017, and it was therefore not progressed to Evidence Synthesis. Soini 2014 was a robust nationwide cohort study with adjustment for key confounding variables for which we prepared a full summary and critical appraisal. Soini 2014 found an increased risk of breast cancer with levonorgestrel-releasing intrauterine system which we considered Low certainty evidence. We considered this evidence to be of comparable reliability to that of Mørch 2017. However, because the Soini 2014 estimates (standardized incidence ratio 1.19, 95% CI 1.13 to 1.25) were highly consistent with those of Mørch 2017 (RR 1.21, 95% CI 1.11 to 1.33), for simplicity of presentation we focus on the Mørch 2017 estimates in Evidence Synthesis.

Combined estrogen plus progestogen pill (combined oral contraceptives)

Evidence Review

Risk of breast cancer in women using any type of combined oral contraceptive* by duration of use, with never use as reference group (Mørch 2017)

Number of woman-years	Number of breast cancer events	Age-adjusted incidence rate (number of events per 100,000 woman-years)	Adjusted relative risk (95% CI)**	P-value	Certainty (downgrade)
6,424,088	1,935	68	**1.19 (1.13 to 1.26)**	< 0.001	Low (cohort study)

Bolding indicates statistically significant results.

* We have reported RRs for combined oral contraceptives overall only because there was insufficient evidence to conclude a difference in effect across progestin types evaluated (further described in Critical Appraisal).

** Adjusted for age, calendar year, level of education, polycystic ovary syndrome, endometriosis, parity, and family history of premenopausal breast or ovarian cancer.

Evidence Synthesis

Outcome	Approach taken and justification	Results
Breast cancer	**Existing analysis, quantitative expression.** We use the 1 relevant study (Mørch 2017) to estimate the increase in risk associated with use of combined oral contraceptives. Given we are not concerned with the precision of the estimate, we use the point estimate for estimation. The risk for women not using hormonal therapy was approximately 0.55% over 10 years in Mørch 2017. We calculated the absolute risk for use of COCP using this baseline risk and the point estimate for the RR noted above; thus, we estimate 0.55% * 1.19 = 0.65% risk over 10 years for women using a combination oral contraceptive. Although Mørch 2017 is likely a high-quality study in terms of univariate estimates, we acknowledge that the baseline risk of 0.55% (a univariate estimate) is being explicitly used to inform comparative estimates/inferences. Accordingly, we assign it a certainty of Low for evidence synthesis statements for coherence/consistency in reporting.	**10-year risk of breast cancer among women treating their symptoms without hormones may be 0.55%** (Low certainty) **10-year risk of breast cancer among women using combination oral contraceptives may be 0.65%** (Low certainty)

Evidence Synthesis Results

Of 1,000 women who treat their symptoms without hormones, about 6 (0.6%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Of 1,000 women who take a combined oral contraceptive pill, about 7 (0.7%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Progestogen-only products

Because Mørch 2017 served as the source for all progestogen-only compounds, we present this section as "Progestogen-only products" for efficiency and ease of comprehension.

Evidence Review

Risk of breast cancer among women with current or recent use of progestogen-only products, with never use as reference group (Mørch 2017)

Contraceptive type	Number of woman-years	No. breast cancer events	Age-adjusted incidence rate (no. events per 100,000 woman-years)	Adjusted relative risk (95% CI)*	Certainty (downgrade)
oral contraceptives					
norethisterone	128,848	78	58	1.00 (0.80 to 1.25)	Very low (cohort study, imprecision)
levonorgestrel	10,547	16	102	**1.93 (1.18 to 3.16)**	Low (cohort study)
desogestrel	77,847	42	69	1.18 (0.87 to 1.60)	Very low (cohort study, imprecision)
nonoral contraceptives					
implant	42,217	9	46	0.93 (0.48 to 1.79)	Very low (cohort study, imprecision)
levonorgestrel-releasing intrauterine system	503,441	571	70	**1.21 (1.11 to 1.33)**	Low (cohort study)
depot medroxyprogesterone acetate	19,308	5	51	0.95 (0.40 to 2.29)	Very low (cohort study, imprecision)

* Relative risks were adjusted for age, calendar year, level of education, polycystic ovary syndrome, endometriosis, parity, and family history of premenopausal breast or ovarian cancer.

Evidence Synthesis

Option (outcome is breast cancer risk)	Approach taken and justification	Results
oral		
norethisterone	**Set risk as equal to women who do not use hormonal therapy.** We use Mørch 2017 to estimate risk of breast cancer in women using norethisterone, which found no significant increase. Therefore, for evidence synthesis, we set this risk as being equal to the risk in Mørch 2017 among women who did not use any hormonal therapy (0.55% over 10 years).	**10-year risk of breast cancer among women taking norethistrone may be 0.55%** (Very low certainty)
levonorgestrel	**Existing analysis, quantitative expression.** We use Mørch 2017 to estimate risk of breast cancer in women using levonorgestrel. Because the CI for the RR is somewhat wide, we favor reporting the increase in risk as a range associated with the lower and upper 95% CIs of the RRs from this study (RRs of 1.18 and 3.16) rather than a point estimate, which could imply greater precision than actually exists (though we note absolute risks are likely to be small in general given the low baseline risk) The risk for women not using hormonal therapy was approximately 0.55% over 10 years in Mørch 2017. We calculated the absolute risk for use of COCP using this baseline risk and the above-noted RRs; thus, we estimate 0.55% * 1.18 = 0.65% and 0.55% * 3.16 = 1.74%.	**10-year risk of breast cancer among women taking levonorgestrel may be 0.65% to 1.74%** (Low certainty)
desogestrel	**Set risk as equal to women who do not use hormonal therapy.** We use Mørch 2017 to estimate risk of breast cancer in women using desogestrel, which found no significant increase. Therefore, for evidence synthesis, we set this risk as being equal to the risk in Mørch 2017 among women who did not use any hormonal therapy (0.55% over 10 years).	**10-year risk of breast cancer among women taking desogestrel may be 0.55%** (Very low certainty)
nonoral		
implant	**Set risk as equal to women who do not use hormonal therapy.** We use Mørch 2017 to estimate risk of breast cancer in women using an implant, which found no significant increase. Therefore, for evidence synthesis, we set this risk as being equal to the risk in Mørch 2017 among women who did not use any hormonal therapy (0.55% over 10 years).	**10-year risk of breast cancer among women using a progestogen implant may be 0.55%** (Very low certainty)

levonorgestrel intrauterine system	**Existing analysis, quantitative expression.** We use Mørch 2017 to estimate risk of breast cancer in women using a levonorgestrel intrauterine system. The relative effect estimate is precise (RR 1.21, 95% CI 1.11 to 1.33), so we use the point estimate for the RR and the baseline risk among women who had not used any hormonal treatment (0.55% over 10 years) to estimate the 10-year risk among women using a levonorgestrel intrauterine system: 0.55% * 1.21 = 0.67%.	**10-year risk of breast cancer among women using a levonorgestrel intrauterine system may be 0.67%** (Low certainty)
depot medroxyprogesterone acetate (DMPA)	**Set risk as equal to women who do not use hormonal therapy.** We use Mørch 2017 to estimate risk of breast cancer in women using DMPA, which found no significant increase. Therefore, for evidence synthesis, we set this risk as being equal to the risk in Mørch 2017 among women who did not use any hormonal therapy (0.55% over 10 years).	**10-year risk of breast cancer among women using a progestogen injection may be 0.55%** (Very low certainty)

We also repeat the synthesis statement for women who do not use hormone-based treatment (described in more detail in the section on combination oral contraceptives) for reference.

Evidence Synthesis Results

Of 1,000 women who treat their symptoms without hormones, about 6 (0.6%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Of 1,000 women who use a progestogen pill, 6 (0.6%) to 7 (0.7%) may get breast cancer over the next 10 years. The risk may be 6 out of 1,000 (0.6%) if the progestogen is norethisterone or desogestrel and 7 out of 1,000 (0.7%) if the progestogen is levonorgestrel. (Low to Very low certainty based on 1 cohort study [Mørch 2017])

Of 1,000 women who use a progestogen injection, about 6 (0.6%) may get breast cancer over the next 10 years. (Very low certainty based on 1 cohort study [Mørch 2017])

Of 1,000 women who use a progestogen intrauterine system, about 7 (0.7%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Of 1,000 women who use a progestogen implant, about 6 (0.6%) may get breast cancer over the next 10 years. (Very low certainty based on 1 cohort study [Mørch 2017])

Gonadotropin releasing hormone analogue/agonist injection/depot

Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)

As noted in FAQ 1, despite their name, continuous use of a gonadotropin releasing hormone agonist actually results in a hypoestrogenemic and hypoprogestinemic state. Accordingly, there is little to no reason to think gonadotropin releasing hormone agonist would increase a woman's risk of breast cancer. The lack of systematic reviews dedicated to this risk is therefore unsurprising, but we also conducted a search for original evidence reports, which yielded no original studies. We therefore conclude that use of a gonadotropin releasing hormone agonist may not increase a woman's risk of breast cancer and set this risk as equal to 0.55% over 10 years based on the estimate for women who did not use any hormonal therapy (described in more detail in the section on combination oral contraceptives); because we gave this estimate a Low certainty rating, we apply the same certainty rating here given we are using this estimate for the option of gonadotropin releasing hormone agonist.

Descriptive Summary and Evidence Synthesis Results

Of 1,000 women who treat their symptoms without hormones, about 6 (0.6%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Of 1,000 women who use an injection of a gonadotropin-releasing hormone agonist, about 6 (0.6%) may get breast cancer over the next 10 years. (Low certainty based on 1 cohort study [Mørch 2017])

Evidence report for hormonal treatment of endometriosis

Search and Selection

Prepared by EBSCO Information Services

November 18, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews or guidelines that involve a systematic review that are more recent than those identified in first-round searching.

Third-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Fourth-round searching will involve citation tracing from sources found in the preceding rounds of searching. This may be done to identify additional evidence sources if the results from the preceding rounds of searching are insufficient.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

FAQ Summary

Results

First-round searching – DynaMed

DynaMed subsection	Number of article citations	Number of unique references included
Endometriosis topic, Guidelines and Resources section, Guidelines subsection (November 18, 2019)	23	1 (NICE 2017)
Oral Contraceptives topic, Oral Contraceptives and Cancer section, Breast cancer subsection	16	1 (Mørch 2017)*

* This section also contains the well-known and highly-cited 1996 Lancet individual patient data meta-analysis, but we did not include it for Critical Appraisal or Evidence Synthesis because of its very dated nature. Indeed, Mørch 2017 explicitly notes a motivating reason for their study was to provide contemporary data on breast cancer risk, and this is relevant in the context of different formulations for combination oral contraceptives (e.g., different estrogen doses) and different types of hormonal contraception (e.g., levonorgestrel intrauterine system) now being used/available.

Second-round searching – searches for intervention-specific systematic reviews

Database	Search string	Number of search results	Number of references included
PubMed November 19, 2019	endometriosis[ti] AND (contraceptive OR contraception OR estrogen OR progestogen OR progestin OR mini-pill OR mini pill OR intrauterine device OR gonadotropin releasing hormone) AND systematic[sb] AND ("2016/11/01"[PDAT] : "3000/12/31"[PDAT])	14	3 (Grandi 2019, Brown 2018, Jensen 2018)
PubMed November 19, 2019	(contraceptive OR contraception OR estrogen OR progestogen OR progestin OR mini-pill OR mini pill OR intrauterine device OR gonadotropin releasing hormone) AND (breast cancer[tiab] OR thromboemboli*[tiab] OR deep venous thrombo*[tiab] OR deep vein thrombo*[tiab] OR pulmonary emboli*[tiab]) AND systematic[sb] NOT (prostate cancer OR receptor OR chemotherapy OR polycystic ovar*)	77	5 (Bergendal 2009*, Dragoman 2018, Oedingen 2018†, Samson 2016, Tepper 2016)

* All 5 studies included in Bergendal 2009 are also included in the more current Tepper 2016, so we do not summarize/appraise or utilize Bergendal 2009 in this evidence report other than to note it is functionally supplanted by Tepper 2016

† Oedingen 2018's results are consistent with Dragoman 2018's results, so we do not summarize/appraise or utilize Oedingen 2018 in this evidence report other than noting its consistency with Dragoman 2018.

Third-round searching – searches for original evidence reports

Database	Search string	Number of search results	Number of references included
PubMed November 26, 2019	(gonadotropin releasing hormone[tiab] OR gonadotropin-releasing hormone[tiab]) AND (breast cancer[tiab] OR thromboemboli*[tiab] OR deep venous thrombo*[tiab] OR deep vein thrombo*[tiab] OR pulmonary emboli*[tiab]) NOT (prostate cancer OR receptor OR chemotherapy OR polycystic ovar*)	43	0*

* Despite their name, continuous administration of GnRH agonists in women with endometriosis actually induces a hypoestrogenemic and -progestinemic state due to downregulation of GnRH receptors and pituitary desensitization. Accordingly, there is little to no reason to think GnRH agonists would increase a woman's risk of thromboembolic events or breast cancer. The lack of systematic reviews dedicated to these risks is therefore unsurprising, but we also conducted a search for original evidence reports, which yielded much the same, aside from 2 case reports purporting to attribute a thromboembolic event to the use of a GnRH agonist. Although we do not dismiss case reports as being entirely unhelpful, we do not consider case reports to have sufficient evidentiary strength to be included in evidence reports.

Fourth-round searching – citation tracing

Source	Tracing	Number of references included
Mørch 2017	Citation tracing for articles of additional relevance	1 (Soini 2014)
Brown 2018	Citation tracing to confirm details of included studies	2 (Harada 2008, Harada 2017)*
Dragoman 2018	Citation tracing for articles of additional relevance	1 (Lidegaard 2009)
Samson 2016	Citation tracing to confirm details of included study	1 (Backman 2005)†
Soini 2014	Citation tracing for articles of additional relevance	1 (Dinger 2011)†

* Incorporated into summary for Brown 2018

† Incorporated into summary for Samson 2016

Search summary:

Number of articles screened and selected

	Screened	Selected*
1st-round (DynaMed)	39	2
2nd-round (Systematic review searches)	91	8
3rd-round (Original article searches)	43	0
4th-round (Citation tracing)	6	6
Total	*179*	*16*†

* Number shown is after deduplication

† For ease of comprehension and efficiency, we do not include all references in Critical Appraisal or Evidence Synthesis. This is due to sources being functionally supplanted by more current sources, sources giving consistent findings with other sources, sources being consulted to clarify details in other sources, and the like.

	Articles selected for evaluation (Author Year)
Systematic reviews	9 (Bergendal 2009*, Brown 2018†, Dragoman 2018‡, Grandi 2019§, Jensen 2018, NICE 2017, Oedingen 2018¶, Samson 2016, Tepper 2016)
Randomized, controlled trials	2 (Harada 2008, Harada 2017)**
Other article types	5 (Backman 2005††, Dinger 2011§, Lidegaard 2009, Mørch 2017, Soini 2014 [all observational studies])

* All 5 studies included in Bergendal 2009 are also included in the more current Tepper 2016, so we do not summarize/appraise or utilize Bergendal 2009 in this evidence report other than to note it is functionally supplanted by Tepper 2016.

† Systematic review of randomized, controlled trials

‡ Systematic review of observational studies

§ Systematic review of randomized, controlled trials and observational studies

¶ Oedingen 2018's results are consistent with Dragoman 2018's results, so we do not summarize/appraise or utilize Oedingen 2018 in this evidence report other than noting its consistency with Dragoman 2018.

** Harada 2008 and Harada 2017 are incorporated into the summary for Brown 2018.

†† Backman 2005 and Dinger 2011 are incorporated into the summary for Samson 2016.

Evidence report for hormonal treatment of endometriosis

Critical Appraisal

Prepared by EBSCO Information Services

November 18, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

FAQ Summary

FAQ 1: What does the treatment involve?

FAQ 2: Will my pain get better?

FAQ 3: Will my quality of life get better?

FAQ 4: What are the side effects or risks?

Results

Characteristics and Results of Critically Appraised Studies/Sources

BROWN 2018

Brown J, Crawford TJ, Datta S, Prentice A. Oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev. 2018 May 22;5:CD001019. PubMed

Relevant to FAQ2

- **Study design:** systematic review of randomized trials
- **Population:** women of reproductive age with symptoms ascribed to a surgically-confirmed diagnosis of endometriosis
- **Intervention:** combined oral contraceptive pills
- **Comparison:** placebo/expectant management, other medical therapies (including other hormonal therapies), and conservative surgical treatment

- **Study inclusion criteria:**
  - studies identified in searches of databases from inception to 19 October 2017
  - studies exploring use of hormonal treatment as adjunct to surgery or other medical treatment for endometriosis were excluded

- **Number of studies:** 5
  - 3 trials provided data suitable for analysis
    - 2 compared COCP vs. placebo (Harada 2008, Harada 2017)
      - Brown 2018 notes both Harada 2008 and Harada 2017 "reported that endometriosis was diagnosed by laparoscopy or laparotomy or endometrioma were diagnosed by ultrasound scan or magnetic resonance imaging". Because of this, Brown 2018 included Harada 2017 in its review, but Harada 2017 did not require surgical or imaging confirmation of endometriosis; in fact, most women in Harada 2017 had a clinical, rather than surgical or imaging-based diagnosis. As noted by Harada 2017:
        - "We included patients aged ≥20 years with a clinical diagnosis of endometriosis who had pelvic tenderness, induration in the cul de sac, or uterine immobility, as well as patients diagnosed as having endometriosis by laparotomy/laparoscopy or by the identification of endometriomas." (p799)
        - "Most randomized patients had a clinical diagnosis of endometriosis, with very few cases visually confirmed by laparoscopy." (p800)
    - 1 compared COCP vs. gonadotropin-releasing hormone analogue (goserelin) (Vercellini 1993)

- 2 additional trials (n = 208) were included in this systematic review but did not provide data that were suitable for quantitative analysis (Guzick 2011, Ali 2013)

- **Number of participants:** 612
  - 404 included in the three trials that provided data that were suitable for analysis
- **Duration of follow-up:** Up to 6 months for COCP vs. placebo; up to 12 months for COCP vs. gonadotropin-releasing hormone analogue

- **Results and certainty:**

Combined oral contraceptive pill vs. placebo on pain-related outcomes associated with endometriosis

Outcome or subgroup title	No of studies (patients)	Mean difference (95% CI)	Certainty (reason for downgrade)*
self-reported pain (dysmenorrhea)			
verbal rating scale (range 0 to 3)	1 (96)	-1.30 (-1.84 to -0.76)	Moderate (imprecision†)
visual analogue scale‡§	2 (327)	-23.68 (-28.75 to -18.62)	Moderate (risk of bias¶)

* Our certainty assessments differ from those in the Cochrane review. This was primarily due to differences in judgments for risk of bias. The authors of the Cochrane review assigned two downgrades for Risk of bias for the self-reported pain (dysmenorrhea) outcomes because the "...pharmaceutical company appeared to have been responsible for randomisation of a trial of their own drug" (ie, the Cochrane authors judged the randomization and blinding to be at risk of bias because of the pharmaceutical company involvement); however, we based our risk of bias assessments on the reporting of the methods in the publication and downgraded based on this (as indicated in footnote comments).

† Evidence comprised of single small trial

‡ One of the two trials (Harada 2017) also reported visual analogue scale scores based on comparison of changes from baseline and it showed consistent results as the end of treatment scores analysis; both showed a significant benefit of COCP vs. placebo. There was some lack of clarity about this change from baseline scores analysis including that it included fewer patients than the post-treatment scores analysis (eg, for COCP group, 114 patients were analyzed from Harada 2017 in post-treatment scores analysis but only 65 in change from baseline scores analysis).

§ Brown 2018 indicates the range for Harada 2017 is 0-100 and the range for Harada 2008 is unknown (ie, "No details relating to scale"). Review of full text of Harada 2008 did not provide additional detail, but the results might suggest a 0-100 scale.

¶ Both trials contributing to this analysis (Harada 2008, Harada 2017) used adequate methods of random sequence generation and allocation concealment. For Harada 2017, the Cochrane risk of bias table indicated for "Allocation concealment" domain "Unclear risk" for "Authors' judgement" and "No details." for "Support for judgement"; however, the full-text report of Harada 2017 was consulted, and a centralized method of allocation concealment appeared to be used which suggests adequate allocation concealment. In terms of incomplete outcome data risk of bias domain, for Harada 2008 there were few losses to follow-up and discontinuations, they were equally distributed between groups, and the losses were for similar reasons; however, for Harada 2017, 20% in each group discontinued the study by 24 weeks of treatment and the discontinuations due to adverse events was higher with COCP (12/130 vs. 2/128). Harada 2017 constituted about 70% of the weight for the analysis of dysmenorrhea on the visual analogue scale, so we judged this outcome to be at risk of bias due to incomplete outcome data.

- insufficient evidence to evaluate effects of COCP vs. goserelin based on 1 trial (n = 50) with no blinding and unclear reporting of random sequence generation and allocation concealment, which reported no significant difference between groups in dysmenorrhea at 6 months' follow-up (following 6-month treatment period)

DRAGOMAN 2018
Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. Int J Gynaecol Obstet. 2018 Jun;141(3):287-294. PubMed

Relevant to FAQ4

- **Study design:** systematic review of observational studies
- **Population:** healthy women using progestogen-containing low-dose (< 50 µg ethinyl estradiol) combined oral contraceptives
- **Intervention:** combined oral contraceptives containing progestogens other than levonorgestrel
- **Comparison:** combined oral contraceptives containing levonorgestrel

- **Study inclusion criteria:** study reported venous thromboembolism risk
    - studies were excluded if they reported risk of venous thromboembolism among mixed group of combined oral contraceptives users with different progestogen-containing combined oral contraceptives

- **Number of studies:** 22
    - 17 case-control studies
    - 5 cohort studies
- **Number of participants:** not reported
- **Duration of follow-up:** not reported

- **Results:**

Summary of meta-analyses for risk of venous thromboembolism among users of combined oral contraceptives by progestogen type compared with levonorgestrel as the progestogen type

Analysis	Cyproterone acetate			Desogestrel			Dienogest			Drospirenone			Gestodene			Norgestimate		
	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)	No. studies	I^2, %	RR (95% CI)
overall	n=9	39.9	**2.04 (1.55 to 2.49)**	n= 16	30.1	**1.83 (1.55 to 2.13)**	n=2	52.6	1.46 (0.57 to 5.41)	n=10	66.4	**1.58 (1.12 to 2.14)**	n=12	46.5	**1.67 (1.32 to 2.10)**	n=9	15.1	1.14 (0.94 to 1.32)
exclusion of poor-quality studies	n=8	43.1	**2.05 (1.59 to 2.53)**	n=14	29.7	**1.80 (1.51 to 2.08)**	n=1	NA	1.10 (0.54 to 2.25)	n=9	70.1	**1.58 (1.10 to 2.18)**	n=11	46.7	**1.63 (1.28 to 2.04)**	n=8	12.0	1.13 (0.91 to 1.31)

RR = risk ratio

Bolding indicates statistically significant results. Results were generally consistent across multiple subgroup analyses.

To make these results more meaningful for an individual patient, a baseline risk is needed, which can then be used in conjunction with the above-noted relative effect estimates. Accordingly, we used the control group data (i.e., data for the levonorgestrel group) from the Lidegaard study included in Dragoman (a summary of the Lidegaard study also appears below), as this is a large and representative cohort study. It would be inappropriate to try to calculate risk from all the studies in the forest plots in Dragoman, because Dragoman also included case-control studies, and incidence cannot be soundly estimated from case-control studies. Because the events in Lidegaard were reported per woman-years of follow-up rather than per number of women, we transformed this into a risk over 10 years for an individual woman in the standard fashion. Whether one uses a linear or exponential method, the risk is approximately 0.55% over 10 years.

Certainty*:

- for effects of combined oral contraceptives containing following progestogen types (vs. levonorgestrel): cyproterone acetate, desogestrel, drospirenone, gestodene, norgestimate
    - Low certainty with downgrade for observational study design
- for effects of combined oral contraceptives containing dienogest (vs. levonorgestrel)
    - Very low certainty with downgrades for observational study design and imprecision

*Although statistical heterogeneity was present in some analyses, we did not downgrade on this for two reasons: 1) it was not clear if this was qualitative heterogeneity or only quantitative heterogeneity, and 2) despite the presence of heterogeneity the findings were generally consistent in the subgroup and sensitivity analyses.

Risk ratios (95% CIs) (unadjusted) for venous thromboembolism among users of combined oral contraceptives by progestogen type compared with levonorgestrel in published meta-analyses*

Author year	Cyproterone	Desogestrel	Dienogest	Drospirenone	Gestodene	Norgestimate
Present analysis	**2.04 (1.55 to 2.49)**	**1.83 (1.55 to 2.13)**	1.46 (0.57 to 5.41)	**1.58 (1.12 to 2.14)**	**1.67 (1.32 to 2.10)**	1.14 (0.94 to 1.32)
Bateson 2016						
Prospective cohort studies	—	—	—	0.94 (0.75 to 1.18)	—	—
Retrospective cohort studies	—	—	—	**1.82 (1.60 to 2.06)**	—	—
Stegeman 2013	**1.6 (1.1 to 2.2)**	**1.8 (1.4 to 2.2)**	—	**1.6 (1.2 to 2.1)**	**1.5 (1.2 to 2.0)**	1.0 (0.7 to 1.3)
Martinez 2012						
RR	—	**1.93 (1.31 to 2.85)**	—	**1.67 (1.10 to 2.55)**	**1.33 (1.08 to 1.63)**	—
OR	**1.65 (1.30 to 2.11)**	**1.62 (1.33 to 1.97)**	—	—	**1.49 (1.13 to 1.96)**	1.11 (0.84 to 1.46)
Kemmeren 2001	—	**1.7 (1.2 to 2.6)**	—	—	**1.5 (1.2 to 2.4)**	—

Bolding indicates statistically significant results.

*Dragoman et al reported that each meta-analysis used different methods and varied in individual studies included, but their findings were generally similar

- **Other considerations:**
  - another recent SRMA (Oedingen 2018) had consistent results
    - used levonorgestrel with 30 to 40 µg ethinylestradiol as reference, and found significantly increased overall risk of VTE for all other combined oral contraceptives they evaluated which included the following (all with 30 to 40 µg ethinylestradiol): desogestrel, drospirenone, gestodene and cyproterone
    - did not include norgestimate in their analysis because "...this progestogen is rarely used, especially in France and Germany" and did not consider dienogest "because of few studies and insufficient data"

GRANDI 2019
Grandi G, Barra F, Ferrero S, Sileo FG, Bertucci E, Napolitano A, Facchinetti F. Hormonal contraception in women with endometriosis: a systematic review. Eur J Contracept Reprod Health Care. 2019 Feb;24(1):61-70. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** systematic review of randomized trials and observational studies
- **Population:** women with validated endometriosis diagnosis
- **Intervention:** hormonal contraceptive therapies
    - included combined hormonal contraceptives, combined oral contraceptives, progestin-only pills, and progestin-only contraceptives
- **Comparison:** placebo, other hormonal therapies, or comparator therapies

- **Study inclusion criteria:** no additional

- **Number of studies:** 3
    - There were 28 studies that met the inclusion criteria for this review, but we limited our extraction to randomized trials comparing a hormonal therapy vs. placebo or expectant management which we had not previously identified in the Brown 2010 Cochrane review (or the Jensen 2018 systematic review, summarized briefly within the Brown 2010 summary) or the 2017 NICE guideline; we identified three relevant randomized trials not previously identified all of which compared LNG-IUS vs. expectant management and this summary focuses on only those three trials. However, we do note that the authors also note there "is insufficient evidence … to reach definitive conclusions about the overall superiority of any particular hormonal contraceptive", which is consistent with conclusions from Jensen 2018 (addressed as part of the summary for Brown 2018) and NICE 2017.
- **Number of participants:** 175
    - as noted in Table 2, the three studies included 40, 55, and 80 patients
- **Duration of follow-up:** 48 to 120 weeks
    - for 3 studies of interest

- **Results and certainty:**

    - **Results from each of 3 trials comparing LNG-IUS vs. expectant management**
        - 1 trial (Vercellini 2003) with 40 women with moderate or severe dysmenorrhea related to endometriosis who had first-line operative laparoscopy reported that moderate or severe dysmenorrhea recurred in 10% of women in postoperative

LNG-IUS group vs. 45% in surgery-only group at 48 weeks after surgery. Although not reported by Grandi 2019, these values amount to an absolute risk difference of -35% (95% CI -7.21% to -57%); p = 0.03 by Fisher's exact method.

- 1 trial (Tanmahasamut 2012) with 55 women with moderate or severe dysmenorrhea related to endometriosis who had laparoscopic conservative surgery reported greater decrease in dysmenorrhea and pelvic pain VAS scores but comparable reduction in dyspareunia VAS score in postoperative LNG-IUS group vs. surgery-only group at 48 weeks after surgery
  - Grandi 2019 also qualitatively notes this trial reported SF-36 scores for quality of life (with the LNG-IUS having "improved" quality of life whereas it "did not change" in the expectant management group); however, it only measured change in SF-36 from baseline (rather than a difference between the groups at a defined time point) and no quantified estimates or inferential statistics are given; and this is a single, small trial.
- 1 trial (Chen 2017) with 80 women with endometriosis who had laparoscopic cystectomy followed by 24 weeks of gonadotropin-releasing hormone agonist treatment reported significantly lower recurrence of dysmenorrhea and greater decrease in dysmenorrhea and non-cyclical pelvic pain VAS scores in postoperative LNG-IUS group vs. surgery-only group at 120 weeks after surgery

- **Downgrades and Certainty of overall body of evidence of 3 trials considered together for dysmenorrhea**
  - Downgrades
    - We assigned a risk of bias downgrade because all 3 trials lacked blinding
    - We did not assign an imprecision downgrade because even though each of the 3 individual trials was relatively small, the overall body of evidence did not warrant an imprecision downgrade
  - Certainty
    - We rated the evidence as Moderate certainty with downgrade only for risk of bias
- **Other considerations**
  - Although we limited this summary to those studies comparing LNG-IUS to expectant management, as noted above, the authors also found there "is insufficient evidence … to reach definitive conclusions about the overall superiority of any particular hormonal contraceptive", which is consistent with conclusions from Jensen 2018 (addressed as part of the summary for Brown 2018) and NICE 2017.
  - This systematic review also claims to demonstrate that combined oral contraceptives and progestin-only treatments lead to "improvement from baseline in QoL [quality of life]". However, we consider the following to be important limitations to such a claim (example citations given where relevant, though they are not necessarily an exhaustive list):
    - their claim concerns improvements from baseline (rather than between-group differences at a set time)
    - many are observational studies (Scala 2018, Morotti 2014, Grandi 2015)
    - there is concerningly-discrepant information about the number of trials included in their review (e.g., compare Tables 1 and 2 to their "Limitations" section)
    - not reporting on quality of life at all (Vercellini 2008)

- only reporting on an outcome for which "quality of life" would arguably be an inappropriately broad application of the construct (Muzii 2011, where the closest outcome we found was a categorical rating of treatment satisfaction)

JENSEN 2018

Jensen JT, Schlaff W, Gordon K. Use of combined hormonal contraceptives for the treatment of endometriosis-related pain: a systematic review of the evidence. Fertil Steril. 2018 Jul 1;110(1):137-152.e1. doi: 10.1016/j.fertnstert.2018.03.012. Epub 2018 Jun 21. PubMed

Relevant to FAQ2, FAQ3

We present a brief summary here of this systematic review to note:

- It did not identify any additional placebo-controlled or expectant-management-controlled trials compared with Brown 2018
- It concluded "insufficient data exist to reach conclusions about the overall superiority of any given CHC [combined hormonal contraceptive] therapy, and the relative benefit in comparison to other approaches."
- It noted that 3 randomized trials (Di Francesco 2014, n = 30, COCP vs. leuprolide; Vercellini 2002, n = 90, COCP vs. oral cyproterone; Zupi 2004, n = 133, COCP vs. leuprolide vs. leuprolide + transdermal ethinyl estradiol and oral norethindrone) measured quality of life as a change from baseline. The authors conclude "Taken together, the findings from the RCTs support that QoL [quality of life] is improved with cyclic combined OC [oral contraceptives], continuous combined OC, GnRH agonist, and oral progestin treatment", but without any "consistent significant differences" between treatments.
    - The authors opined the quality of the evidence was low, citing issues pertaining to the paucity of placebo-controlled trials, lack of blinding, and the like. We would additionally downgrade the results to Very low certainty due to the quality of life measurements being assessed as a change from baseline and due to some of the results having statistically-significant, but clinically-questionable degrees of change. For instance, Di Francesco 2014 is noted as showing a change from 39.5 to 46 and 46.9 to 49 (on a scale from 0 to 100) for COCP and GnRH agonist, respectively. These are both considered statistically significant, but the clinical relevance of a 6.5-point and 2.1-point difference (out of 100) is very questionable. We also note that Zupi 2004 did not show any significant differences compared to baseline for either COCP or leuprolide (only the arm receiving leuprolide plus transdermal ethinyl estradiol and oral norethindrone showed benefit compared to baseline for certain quality of life domains, but not others).

LIDEGAARD 2009

Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ. 2009 Aug 13;339:b2890. PubMed

Relevant to FAQ4

- **Study design:** observational study
  - national cohort study in Denmark, 1995 to 2005
  - nationwide registries provided individually updated information on hormonal contraception use, venous thrombosis diagnoses, and potential confounders
- **Population:** non-pregnant Danish women aged 15 to 49 with no history of malignant disease or cardiovascular events
  - women with cancer and cardiovascular diseases were excluded because of their increased risk for venous thrombosis, their decreased probability of using combined oral contraceptives, and because the aim of the study was to assess risk for a first ever thrombotic event
- **Intervention:** different types of hormonal contraception
  - focus was on regimen, estrogen dose, type of progestogen, and route of administration
- **Comparison:** no hormonal contraception or hormonal contraception of different type than that used in intervention group
  - comparison differed depending on outcome evaluated
  - for comparison of use vs. non-use of oral contraceptives, the non-use comparison group was defined to include both never users and former users both because never users are an increasingly selected group of women and some women who were categorized as never users in the study window may have been users prior to 1995

- **Study inclusion criteria:** no additional

- **Number of studies:** not applicable
- **Number of participants:** 10.4 million women years of observation
  - 3.4 million woman-years of current use
  - 2.3 million woman-years of former use
  - 4.8 million woman-years of never use
- **Duration of follow-up:** study period was 11 years

- **Results:**

Crude incidence rates and adjusted rate ratios of venous thromboembolism in women using different types of hormonal contraception (with non-users as reference standard)

Characteristic	Woman-years	% of woman-years	Number of women with venous thrombosis	Rate per 10,000 woman years	Adjusted rate ratio (95% CI)	Certainty (downgrade)
use of combined pill:						
< 1 year	684,061	21.6	443	6.48	**4.17 (95% CI 3.73 to 4.66)***	Low (cohort study†)
1 to 4 years	1,449,000	45.8	787	5.43	**2.98 (95% CI 2.73 to 3.26)***	Low (cohort study†)
> 4 years	1,031,953	32.6	793	7.68	**2.76 (95% CI 2.53 to 3.02)***	Low (cohort study†)
oral contraceptives with 50 µg estrogen	82,902	2.5	65	7.84	**2.67 (95% CI 2.09 to 3.42)***	Low (cohort study†)
oral contraceptives with 20-40 µg estrogen plus:						
levonorgestrel	367,408	10.9	201	5.47	**2.02 (95% CI 1.75 to 2.34)***	Low (cohort study†)
desogestrel or gestodene	2,008,262	59.8	1370	6.82	**3.55 (95% CI 3.30 to 3.83)***	Low (cohort study†)
drospirenone	131,541	3.9	103	7.83	**4.00 (95% CI 3.26 to 4.91)***	Low (cohort study†)
progestogen only:						
levonorgestrel 30 µg or norethisterone 350 µg	65,820	0.6	12	1.82	0.59 (95% CI 0.33 to 1.04)*	Very low (cohort study†, imprecision)
desogestrel 75 µg	9,044	0.1	3	3.32	1.10 (95% CI 0.35 to 3.41)*	Very low (cohort study†, imprecision)
hormone releasing intrauterine device	101,351	1	34	3.35	0.89 (95% CI 0.64 to 1.26)	Very low (cohort study†, imprecision)

Bolding indicates statistically significant results.

*Adjusted for age, calendar year, and educational level

†Authors pointed out in their Discussion section that a potential limitation of their study was lack of two potential confounders: 1) family predisposition and 2) body mass index; however, they provided a reasonable explanation that these would be unlikely to substantially bias rate ratios.

Crude incidence rates and adjusted* rate ratios (95% confidence intervals) of venous thromboembolism in current users of combined oral contraceptives according to dose of estrogen and type of progestogen

	Progestogen						
Variable	**Norethisterone**	**Levonorgestrel**	**Norgestimate**	**Desogestrel**	**Gestodene**	**Drospirenone**	**Cyproterone**
estrogen 50 µg:	1.44 (0.97 to 2.14)	1.20 (0.85 to 1.71)	-	-	-	-	-
woman years	39,211	43,691	-	-	-	-	-
VTE	28	37	-	-	-	-	-
estrogen 30 to 40 µg:	0.98 (0.71 to 1.37)	1 (reference)	1.19 (0.96 to 1.47)	**1.82 (1.49 to 2.22)**	**1.86 (1.59 to 2.18)**	**1.64 (1.27 to 2.10)**	**1.88 (1.47 to 2.42)**
woman years	118,751	367,408	329,463	233,883	1,012,977	131,541	126,687
VTE	43	201	151	191	744	103	90
estrogen 20 µg:	-	-	-	1.51 (1.25 to 1.82)	1.51 (1.22 to 1.86)	-	-
woman years	-	-	-	442,223	319,180	-	-
VTE	-	-	-	251	184	-	-

VTE = venous thromboembolism
Bolding indicates statistically significant results.
*Rate ratios adjusted for age, calendar year, education, and length of use.

- **Certainty**:
  - Low certainty for increased risk of VTE in current users of combined oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone vs. levonorgestrel as progestogen type (downgrade because of cohort study)

- **Other considerations**:
  - This was one of the studies included in Dragoman 2018 SRMA summarized above. The results of the SRMA were consistent with the results of Lidegaard 2009, both finding that combined oral contraceptives with gestodene, desogestrel, cyproterone acetate

and drospirenone had similar risks for VTE, which were significantly higher than risk with levonorgestrel as progesterone component of combined pill.

- To make these results more meaningful for an individual patient, a baseline risk is needed, which can then be used in conjunction with the above-noted relative effect estimates. Accordingly, we used the control group data (i.e., data for the non-users group). Because the events in Lidegaard 2009 were reported per woman-years of follow-up rather than per number of women (3.01 events per 10,000 woman-years, based on 2,168 events over 7,194,242 woman-years), we transformed this into a risk over 10 years for an individual woman in the standard fashion. Whether one uses a linear or exponential method, the risk is approximately 0.30% over 10 years.
- As noted in the summary for Dragoman 2018, the results from Lidegaard 2009 yield an estimated 10-year risk of 0.55% for VTE among women taking a levonorgestrel-containing COC.
- This was also one of the studies included in Tepper 2016 SRMA summarized below. Lidegaard 2009 was one of 2 studies in Tepper 2016 for which results were reported for specific progestin-only pills (the other was Lidegaard 2011) and both studies considered together find Very low certainty evidence of no important increase in VTE for any specific progestin-only pill evaluated. Lidegaard 2009 was also consistent with Tepper 2016 in finding no important increase in VTE with hormone releasing intrauterine device; Lidegaard 2009 was 1 of 5 studies in Tepper 2016 comparing women using levonorgestrel-releasing intrauterine system vs. nonusers and none showed increase risk in venous thromboembolism (and in all 5, the point estimate favored decreased risk).

MØRCH 2017

Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary Hormonal Contraception and the Risk of Breast Cancer. N Engl J Med. 2017 Dec 7;377(23):2228-2239. PubMed

Relevant to FAQ4

- **Study design:** observational study
  - national cohort study in Denmark, 1995 to 2012
  - nationwide registries provided individually updated information on hormonal contraception use, breast-cancer diagnoses, and potential confounders
    - cancer risk-related potential confounders that were adjusted for included age, calendar year, education, parity, polycystic ovary syndrome, endometriosis, and family history of breast or ovarian cancer; additionally, adjustment for body-mass index, smoking status, and age of woman at first delivery was made when this information was recorded for parous women
- **Population:** Danish women aged 15 to 49 with no history of cancer or venous thromboembolism and no prior treatment for infertility

- **Intervention:** current and recent (≤ 6 months) use of hormonal contraception
- **Comparison:** never use of hormonal contraception

- **Study inclusion criteria:** no additional

- **Number of studies:** not applicable
- **Number of participants:** 1.8 million women who were followed mean 10.9 years (19.6 million person-years total)
- **Duration of follow-up:** mean 10.9 years

- **Results:**

Risk of breast cancer in women using any type of combined oral contraceptive by duration of use (with never use as reference group)*

Duration of (current or recent) use	Number of woman-years	Number of breast cancer events	Age-adjusted incidence rate (number of events per 100,000 woman-years)	Adjusted relative risk (95% CI)†	P-value	Age-adjusted risk difference (95% CI) per 100,000 woman-years	Certainty (downgrade)
overall	6,424,088	1,935	68	**1.19 (1.13 to 1.26)**	< 0.001	**13 (10 to 17)**	Low (cohort study)
< 1 year	1,084,435	194	54	1.03 (0.89 to 1.19)		−1 (−8 to 8)	Very low (cohort study, imprecision)
1 to < 5 years	2,980,688	603	64	**1.17 (1.07 to 1.27)**		**9 (3 to 14)**	Low (cohort study)
5 to 10 years	1,808,425	652	70	**1.27 (1.16 to 1.38)**		**15 (8 to 21)**	Low (cohort study)
> 10 years	550,540	486	76	**1.46 (1.32 to 1.61)**		**21 (14 to 28)**	Low (cohort study)

Bolding indicates statistically significant results.

Mørch 2017 also reported RRs at 4 time ranges since last use of hormonal contraception (ie, < 1 year, 1 to < 5 years, 5 to 10 years, and > 10 years) for both 'Any hormonal contraception' group and 'Combined oral contraceptives' group and there were similar effects at different time ranges for both.

* In addition to reporting data for use of any type of "combined oral contraceptive" vs. never use, Mørch 2017 also reported data for use of "any hormonal contraception" vs. never use (also stratified by duration of use). However, we only extracted data for "combined oral contraceptive" to allow us to report effects per treatment option (combined oral contraceptives is one of the options of interest for this evidence report). For progestogen-only products (oral and non-oral), effects stratified by duration of use are reported only for levonorgestrel-releasing intrauterine system (and summarized in footnote of table below). "Any hormonal contraceptive" is too broad to be meaningful for this evidence report.

† Relative risks were adjusted for age, calendar year, level of education, polycystic ovary syndrome, endometriosis, parity, and family history of premenopausal breast or ovarian cancer.

Risk of breast cancer among women using various types of hormonal contraception (with never use as reference group)

Variable	Number of woman-years	No. breast cancer events	Age-adjusted incidence rate (no. events per 100,000 woman-years)	Adjusted relative risk (95% CI)*	Age-adjusted risk difference (95% CI) per 100,000 woman-years	Certainty (downgrade)
current or recent use of combined hormonal contraception						
oral combined ethinyl estradiol, 50 µg						
norethisterone	52,895	23	46	1.01 (0.67 to 1.52)	−9 (−30 to 12)	Very low (cohort study, imprecision)
levonorgestrel	73,125	54	64	1.21 (0.93 to 1.59)	9 (−9 to 27)	Very low (cohort study, imprecision)
oral combined ethinyl estradiol, 20 to 40 µg						
norethisterone	153,603	39	67	1.09 (0.80 to 1.50)	12 (−12 to 35)	Very low (cohort study, imprecision)
levonorgestrel	638,936	380	72	**1.33 (1.20 to 1.48)**	**17 (9 to 25)**	Low (cohort study)
norgestimate	635,732	180	72	**1.22 (1.20 to 1.48)**	**18 (5 to 30)**	Low (cohort study)
desogestrel	1,453,690	368	64	**1.12 (1.01 to 1.25)**	**9 (1 to 17)**	Low (cohort study)
gestodene	2,633,355	705	69	**1.20 (1.11 to 1.30)**	**14 (8 to 20)**	Low (cohort study)
drospirenone	503,700	102	60	1.05 (0.86 to 1.28)	6 (−8 to 20)	Very low (cohort study, imprecision)
cyproterone	272,804	77	90	**1.44 (1.15 to 1.81)**	**36 (11 to 60)**	Low (cohort study)
estradiol valerate and dienogest	6,380	7	101	1.62 (0.77 to 3.41)	46 (−30 to 122)	Very low (cohort study, imprecision)
current or recent use of progestogen-only products						
oral contraceptive						
norethisterone	128,848	78	58	1.00 (0.80 to 1.25)	3 (−10 to 16)	Very low (cohort study, imprecision)
levonorgestrel	10,547	16	102	**1.93 (1.18 to 3.16)**	47 (−4 to 99)	Low (cohort study)
desogestrel	77,847	42	69	1.18 (0.87 to 1.60)	14 (−8 to 36)	Very low (cohort study,

						imprecision)
nonoral contraceptive						
implant	42,217	9	46	0.93 (0.48 to 1.79)	−9 (−42 to 25)	Very low (cohort study, imprecision)
levonorgestrel-releasing intrauterine system	503,441	571	70	**1.21 (1.11 to 1.33)†**	**16 (9 to 22)**	Low (cohort study)
depot medroxyprogesterone acetate	19,308	5	51	0.95 (0.40 to 2.29)	−4 (−49 to 42)	Very low (cohort study, imprecision)

Bolding indicates statistically significant results.

* Relative risks were adjusted for age, calendar year, level of education, polycystic ovary syndrome, endometriosis, parity, and family history of premenopausal breast or ovarian cancer.

† Increased risk consistent at all four durations of follow-up: < 1 year (adjusted relative risk [RR] 1.37 [95% CI 1.04 to 1.79]); 1 to < 5 years (adjusted RR 1.26 [95% CI 1.10 to 1.43]); 5 to 10 years (adjusted RR 1.27 [95% CI 1.09 to 1.48]); > 10 years (adjusted [RR] 1.25 [95% CI 1.00 to 1.56]). The authors note in Discussion section that the lack of an association between duration of use of levonorgestrel-releasing intrauterine system and breast-cancer risk may be explained by the system providing decreasing dose of progestogen released based on the time since insertion.

- **Other considerations**
  - To make these results more meaningful for an individual patient, a baseline risk is needed, which can then be used in conjunction with the above-noted relative effect estimates. Accordingly, we used the control group data (i.e., data for the group of women who had never used) from this study to estimate the baseline risk among non-users, namely an age-adjusted incidence rate of 55 breast cancer events per 100,000 woman-years (based on 5,955 breast cancer events over 7,815,180 woman-years of follow-up). Because the data are reported as a number of events per 100,000 woman-years, we transformed this into a risk over 10 years in the standard fashion. Whether one uses a linear or exponential method, the risk is approximately 0.55% over 10 years.
  - There was insufficient evidence to conclude on effects of specific progestin types included in combined formula; although estimates for combinations with some types were significant and combinations with others were not, there were no subgroup tests reported and the CIs of the associated estimates all widely overlapped. Therefore, although we have extracted and reported in table above the RR estimates associated with specific progestin-types included in combined formulas, we have carried forward to Synthesis only the overall estimate.
  - As noted in 'Other considerations' bullets in Samson 2016 SR summary, none of the 6 studies in Samson 2016 were progressed to Synthesis; the only other study reporting breast cancer outcome which progressed to synthesis was Soini 2014 which evaluated only the option of levonorgestrel-releasing intrauterine system. The breast cancer risk for all other options was based only on Mørch 2017.

- Authors reported in Discussion section that their findings are consistent with earlier studies evaluating different progestogen types in combined pills
  - collaborative reanalysis of data from individual women found similar increase in breast cancer risk among current users of combined oral products (risk ratio 1.24, 95% CI 1.15 to 1.33) (Lancet 1996)
    - this study was also triaged in Search and Selection, but was not progressed to Critical Appraisal due to its very dated nature; indeed, Mørch 2017 explicitly notes a motivating reason for their study was to provide contemporary data on breast cancer risk, and this is relevant in the context of different formulations for combination oral contraceptives (e.g., different estrogen doses) and different types of hormonal contraception (e.g., levonorgestrel intrauterine system) now being used/available.
  - other studies have also not shown consistent differences among women who used older combined oral contraceptives (from the 1970s and 1980s) that had a different progestin content

NICE 2017

National Guideline Alliance (UK). Endometriosis: diagnosis and management. London: National Institute for Health and Care Excellence (UK); 2017 Sep. PubMed

Relevant to FAQ2, FAQ3

- **Study design:** clinical practice guideline informed by systematic review
  - effectiveness of hormonal medical treatments for treating endometriosis was one of the topics on which guideline made recommendations (1.8 Pharmacological pain management, Recommendations 1.8.5 to 1.8.7 are specific to hormonal medical treatments)
    - relevant evidence underpinning guideline's recommendations was summarized in 'Full guideline', in section 11.1.3 'Hormonal medical treatments' (with relevant detail from this section extracted for summary below)
    - studies meeting eligibility criteria for addressing effects of hormonal treatments were required to be randomized trials with duration $\geq$ 3 months
      - as described in 'Appendix D: Review Protocols', section 'D.10 - Pharmacological, non-pharmacological, surgical and combination management strategies'
- **Population:** women between menarche and menopause with confirmed or suspected endometriosis of any stage, recurrence status, or severity who are having pain
- **Intervention:** hormonal medical treatments
  - any type and administered at any dose, frequency, or treatment duration recommended in British National Formulary, and by any route of administration
    - we extracted for this summary only data specific to the following hormonal treatments, per Scoping

        - combined estrogen oral progestogen oral
        - progestogen oral
        - progestogen injection/depot
        - progestogen intrauterine system
        - progestogen implant/subcutaneous
        - gonadotropin releasing hormone analogue/agonist injection/depot
- **Comparison:** placebo/expectant management or another hormonal treatment
    - trials comparing one hormonal treatment vs. another hormonal treatment could include placebo in each arm to blind for route of administration

- **Study inclusion criteria:** no additional

- **Number of studies:** Varies by outcome
    - 17 randomized trials evaluating hormonal therapy and reporting on pain (as noted in 'Table 71: Summary of included studies' of full guideline)
    - 36 randomized trials evaluating hormonal therapy and reporting discontinuation due to adverse events (p203 of full guideline)
- **Number of participants:** Varies by outcome
    - 1,999 patients included in 17 randomized trials noted above
        - the number of patients in each of the 17 trials in Table 71 was summed to calculate 1,999
    - 5,319 women included in the 36 randomized trials noted above (p203 of full guideline)
- **Duration of follow-up:** duration ≥ 3 months was part of inclusion criteria (as noted above)

- **Results:**

Direct comparisons of hormonal treatment vs. placebo or expectant management for overall pain or dysmenorrhea

Direct comparisons are reported in clinical evidence profile tables in section 11.1.3.3.2. We extracted data from these tables relevant to the comparison of any of our scoped options vs. either placebo or expectant management.

- Table 72 compared GnRH agonist vs. expectant management and Table 73 compared GnRH agonist vs. placebo.
    - Table 72 is comprised of data from a single, very small (n = 35) RCT that compared an intranasal preparation of a GnRH agonist (not an injection or depot) vs. expectant management, so it was not considered further (though its results were consistent with GnRH agonists providing relief from dysmenorrhea).
    - Table 73 showed a reduction in dysmenorrhea at 12 weeks (MD of -6.30 [95% CI -9.93 to -2.67] for dysmenorrhea on an 11-point VAS, based on 1 trial of 88 women [Ling 1999] randomized to IM leuprolide or placebo), but assessment occurred at 3

months and immediately after the treatment period (rather than a longer period/establishing durable treatment/post-treatment effects).

- There was also a table which compared combined oral contraceptive pill vs. placebo (Table 74), but it did not include the recent trial (Harada 2017) and only includes the earlier trial (Harada 2008); therefore, we relied on Brown 2018 for this comparison which includes a meta-analysis of both trials (see Brown 2018 summary).
- There were no tables reporting the comparison of LNG-IUS vs. placebo or expectant management, but we became aware of the existence of 3 trials making a comparison of LNG-IUS vs. expectant management by our review of the Grandi 2019 systematic review, and this comparison is included in the Grandi 2019 summary. One of these trials was published after the search close for the NICE review, and the other two were noted as being excluded due to the trials being conducted in patients who had also had surgical treatment for endometriosis (see Appendix H, Table H.15).

Matrix of mean differences for hormone therapy for pain relief measured on visual analogue scale (0 to 100 scale)

placebo/expectant management	**-12.3 (95% CI -12.7 to -11.9)**				**-18.6 (95% CI -20.4 to -16.8)**
-12.6 (95% CrI -15.3 to -9.8)	***progestogen (oral)***			**1.5 (95% CI 0.7 to 2.3)**	
-13.2 (95% CrI -16.2 to -10.1)	-0.6 (95% CrI -1.8 to 0.6)	***progestogen (i.m.)***			
-17.7 (95% CrI -25.5 to -9.8)	-5.1 (95% CrI -12.8 to 2.7)	-4.5 (95% CrI -12.4 to 3.4)	***progestogen (i.u.)***	-1.4 (95% CI -2.8 to 0.1)	
-15.7 (95% CrI -21.3 to -10.1)	-3.2 (95% CrI -8.5 to 2.2)	-2.6 (95% CrI -8.1 to 2.9)	1.9 (95% CrI -3.4 to 7.3)	***GnRHa (i.m.)***	
-15.1 (95% CrI -20.8 to -9.3)	-2.5 (95% CrI -8.0 to 3.0)	-1.9 (95% CrI -7.6 to 3.7)	2.5 (95% CrI -2.8 to 8.1)	0.7 (95% CrI -0.2 to 1.5)	***progestogen (oral) plus estrogen (oral)***

i.m. = intramuscular; i.u. = intrauterine

Adapted from Table 65 of full NICE guideline, limiting to hormonal treatments scoped for our evidence report.

Results are reported as mean differences between the column-defined and row-defined treatments. Upper right section of table presents results of pairwise meta-analyses (when available) and lower left section of table presents results computed from multivariate network meta-analysis. Numbers in bold are reported for results that show significant difference between interventions. The multivariate network meta-analysis incorporated additional information that permitted establishment of a common scale (visual analogue scale from 0 to 100) for all treatments, even if the contributing evidence was originally measured on a different scale (eg, progestogens i.m., GnRHa i.m., and progestogen oral plus estrogen oral). The NICE review authors did not include pairwise results involving these treatments in this table because they would be reported on different scales. They also noted that multivariable and univariable network meta-analysis results were broadly similar when available for comparisons. The NICE review authors also reported a network meta-analysis for a subset of trials that reported on pain relief specific to dysmenorrhea which included only 1 comparison relevant to our scoped outcome (ie, GnRHa i.m. vs. placebo) and found a significant benefit of GnRHa i.m. vs. placebo on pain relief specific to dysmenorrhea, consistent with the finding of GnRHa i.m. vs. placebo on the 0 to 100 visual analogue scale.

Matrix of odds ratios for hormone therapy for withdrawals due to adverse events

placebo/expectant management	10.19 (95% CI 0.96 to 371)					0.49 (95% CI 0.07 to 3.18)
17.9 (95% CrI 1.76 to 676)	***progestogen (oral)***	1.66 (95% CI 0.15 to 21.3)		0.79 (95% CI 0.12 to 4.95)		
26.8 (95% CrI 2.11 to 999)	1.47 (95% CrI 0.27 to 9.1)	***progestogen (i.m.)***	0.4 (95% CI 0.06 to 2.37)	0.88 (95% CI 0.22 to 3.26)		
10.7 (95% CrI 0.35 to 811)	0.57 (95% CrI 0.03 to 9.32)	0.39 (95% CrI 0.04 to 3.23)	***progestogen (i.u.)***			
17.4 (95% CrI 1.66 to 701)	0.98 (95% CrI 0.23 to 4.23)	0.66 (95% CrI 0.15 to 2.72)	1.71 (95% CrI 0.13 to 24.4)	***GnRHa (i.m.)***		
5.4 (95% CrI 0.34 to 251)	0.3 (95% CrI 0.04 to 1.87)	0.21 (95% CrI 0.02 to 1.59)	0.53 (95% CrI 0.02 to 10.9)	0.31 (95% CrI 0.05 to 1.57)	***GnRHa (s.c.)***	
0.48 (95% CrI 0.04 to 5.53)	**0.03 (95% CrI <0.01 to 0.77)**	**0.02 (95% CrI <0.01 to 0.6)**	0.04 (95% CrI <0.01 to 2.92)	**0.03 (95% CrI <0.01 to 0.81)**	0.09 (95% CrI <0.01 to 3.57)	***progestogen (oral) plus estrogen (oral)***

i.m. = intramuscular; i.u. = intrauterine

Adapted from Table 69 of full NICE guideline, limiting to hormonal treatments scoped for our evidence report.

Results are reported as odds ratios between the column-defined and row-defined treatments. Upper right section of table presents results of pairwise meta-analyses (when available) and lower left section of table presents results computed from network meta-analysis. Numbers in bold are reported for results that show significant difference between interventions.

Results for quality of life

As summarized in section '11.1.3.3.5 Clinical evidence statements', the NICE review found no placebo-controlled/expectant management-controlled trials reporting on quality of life and only 1 small RCT comparing two active treatments scoped for this evidence review (Petta 2005, comparing leuprolide and levonorgestrel intrauterine system; n = 83, but only 68 providing data for the analysis at the 6-month point, with a MD at 6 months of -1.20 [95% CI -7.79 to 5.39] on a 0-110 scale). Due to the insufficient number of studies available, no pairwise or network meta-analyses were performed for quality of life; the NICE review addressed this outcome with simple pairwise comparisons and evidentiary statements as possible.

Certainty: Low for direct estimate of pain (of IM GnRH agonist vs. placebo); Very low for indirect/network estimates of pain and for discontinuation due to adverse events; insufficient evidence for quality of life

- in addition to the outcome-specific downgrades noted below, we also assigned a general reduction in certainty due to the occurrence of several areas where reporting was insufficiently clear or seemingly implausible; examples include:

  - for the outcome of pain reduction for oral progestogens vs. placebo/expectant management, the matrix of results suggests a pairwise result is available, but we were unable to confirm the existence of a trial providing data for such an outcome
  - inexplicable inconsistencies in data extraction for some outcomes (e.g., there were discrepancies in the extracted data for the Fedele 1993 and Bergqvist 1998 trials when we cross-checked them against the cited Brown 2010 Cochrane review; though we note these discrepancies did not result in substantial differences for estimates of comparative effect, we did not cross-check all extracted data, so it is possible additional discrepancies exist that might have more substantive effects)
  - the magnitude of effect sizes for several of the matrix results for withdrawal due to adverse events seem implausible (e.g., the network comparisons for combination progestogen and estrogen versus other agents and versus placebo)
- pain
  - direct estimate of IM GnRH agonist vs. placebo
    - downgrades
      - imprecision – results based on a single, small trial
      - indirectness – measurements of efficacy were taken at 3 months, immediately after the treatment period (rather than a longer period of time/better establishing durability of benefit); the NICE review authors also downgraded for this
  - indirect/network estimates
    - downgrades
      - unclear risk of bias of included trials – risk of bias of trials contributing to comparisons in matrix of results not adequately reported to allow for evaluation
      - indirectness – very limited data providing direct comparisons to placebo/expectant management
        - this is corroborated by the reporting in the NICE review and by our examination of other evidence sources (e.g., Brown 2018, Grandi 2019)
- withdrawals due to adverse events
  - downgrades
    - serious concern for unclear risk of bias -- risk of bias of trials contributing to comparisons in matrix of results not adequately reported to allow for evaluation; NICE review notes 5 studies were at high risk of bias, 21 were at moderate risk of bias, and 10 were at low risk of bias, but does not provide further detail like what was done for the pain outcomes in the clinical evidence profile tables (Tables 72 through 85) that use GRADE certainty rating for efficacy outcomes)
    - serious concern for inconsistency – authors note their estimates are derived from a random-effects model with “very high heterogeneity”, but only report an estimate for between-study SD (0.94 [95% CrI 0.45 to 1.69])
    - serious concern for unclear directness – insufficient reporting to permit satisfactory evaluation of this domain
    - no serious concern above coherence – authors note serious incoherence for some treatments, but none are of relevance for this evidence report; the authors note other closed treatment loops did not have serious incoherence

        - serious concern for imprecision – withdrawals due to adverse events were relatively rare, resulting in low precision of analyses
- quality of life
    - As noted above, the NICE review authors found no placebo-controlled/expectant management-controlled trials reporting on quality of life and only 1 small trial reporting on quality of life that compared two active treatments scoped for this evidence report. The NICE review authors considered this trial to provide Moderate certainty evidence of no clear difference in quality of life between the two treatments. However, we would rate the certainty in this evidence as insufficient given the rather small sample size and the fact that this is a single trial apparently without replication (thus raising concern over a type II error).
    - Perhaps more importantly than the above point, however, is the broader implication concerning how the scoped options might impact quality of life, namely that the evidence base is largely insufficient to permit any meaningful conclusions. Accordingly, rather than any attempt to conclude on the above-noted single trial comparing two specific options, we think a more prudent conclusion is highlighting the insufficiency of the evidence base for this outcome.

- **Other considerations:**
    - We note there is a general paucity of trials conducted against placebo
    - Given the Very low certainty evidence for discontinuation due to adverse events and the concerns we have about plausibility for several of the quantified estimates, we consider it inappropriate to offer quantitative or comparative conclusions; accordingly, we adopt descriptive responses only in Evidence Synthesis
    - As described in section '11.1.3.4.1 Relative value placed on the outcomes considered', the Committee preparing the NICE Report classified considered outcomes as 'critical' or 'important'. Critical outcomes were pain relief, health-related quality of life, and discontinuations due to adverse events, which we have summarized above. Important outcomes (which were considered less clear indicators of effectiveness than critical outcomes) were rate of success, satisfaction with treatment, effect on daily activities, and reduction in size and extent of endometriotic cysts. In section '11.1.3.3.1 Description of clinical evidence', the authors note that no 'important' outcomes were available for trials comparing hormonal treatments vs. placebo; effects on daily activities was noted as the only important outcome available for trials comparing one hormonal treatment vs. another hormonal treatments; and patient satisfaction was noted as the only important outcome available for trials comparing hormonal treatment vs. combined oral contraceptive pill. There was no evidence available for any other 'important' outcomes.

SAMSON 2016

Samson M, Porter N, Orekoya O, Hebert JR, Adams SA, Bennett CL, Steck SE. Progestin and breast cancer risk: a systematic review. Breast Cancer Res Treat. 2016 Jan;155(1):3-12. PubMed

Relevant to FAQ4

- **Study design:** systematic review of observational studies
- **Population:** women using progestin-only contraceptives
- **Intervention:** progestin-only contraceptives
- **Comparison:** dependent on study design
    - for case-control studies, for example, cases were women with breast cancer and controls were women admitted for diagnoses that were independent of contraceptive use and breast cancer risk

- **Study inclusion criteria:**
    - published between 2000 and 2015
        - authors included only studies published after 1999 because their objective was to evaluate association between progestin-only hormonal contraceptives and breast cancer risk since the 1999 International Agency for Research on Cancer Monographs' assessment, which analyzed 8 case-control studies published between 1986 and 1996 in various countries (United Kingdom, United States, France, Kenya, Mexico, Thailand, Denmark, and New Zealand) and found inadequate evidence for the relationship between progestin-only contraceptives (pill, injectable-DMPA) and breast cancer
- **Number of studies:** 6
    - 3 case-control
    - 3 cohort
- **Number of participants:** 217,355
    - 12,189 cases of breast cancer
- **Duration of follow-up:** 9 to 10 years in 2 of 6 studies that reported follow-up duration
    - Backman 2005 - 10 years
    - Fabre 2007 - 9.1 years (mean)

Characteristics of studies evaluating progestin-only formulation exposure and breast cancer risk

Author year	Progestin-only formulation evaluated	Study design	Country*	Age range	Number of women (cases)	Comparative effect for overall association	RR in specific subgroups	Certainty (downgrade)
Shapiro 2000	injections	case-control	South Africa	20–54	2,109 women (484 cases)	RR 0.9 (95% CI: 0.7 to 1.2) (for any use vs. never use across all ages)	consistent effects in specific age group categories	Very low (observational study, imprecision, risk of bias§)

Author year	Progestin-only formulation evaluated	Study design	Country*	Age range	Number of women (cases)	Comparative effect for overall association	RR in specific subgroups	Certainty (downgrade)
Marchbanks 2002	oral progestin (not further defined)	case-control	United States	35–64	11,938 women (4,575 cases)	RR 0.9 (95% CI: Not reported) for current/previous vs. never	aspects of oral contraceptive use revealed no association with breast cancer	Very low (observational study, imprecision, indirectness†)
Fabre 2007	oral progestin (not further defined)	prospective cohort	France	40–64	73,664 women (880 cases)	RR 1.01 (95% CI 0.93 to 1.11) for ever vs. never use	current use > 4.5 years: RR 1.44 (95% CI 1.03 to 2.00)‡; current use < 4.5 years RR 1.09 (95% CI 0.92 to 1.29)	Very low (observational study, indirectness†)
Kumle 2002	oral progestin (not further defined)	prospective cohort	Norway and Sweden	30–49	103,027 women (54 cases)	RR 1.1 (95% CI 0.8 to 1.7) for ever vs. never use	only current/recent use: RR 1.6 (95% CI 1.0 to 2.4)	Very low (observational study, imprecision, indirectness†)

Author year	Progestin-only formulation evaluated	Study design	Country*	Age range	Number of women (cases)	Comparative effect for overall association	RR in specific subgroups	Certainty (downgrade)
Strom 2004	injections or implants	case-control	United States	35–64	9,257 women (4,575 cases)	OR 0.7 (95% CI 0.4 to 1.3) for current use of injections (within 1 year) vs. never use; report also notes "no significant association for women who had ever been exposed to injections or implants" but does not report OR specific to implants		Very low (observational study, imprecision, risk of bias§)
Backman 2005	levonorgestrel-releasing intrauterine system	retrospective cohort	Finland	30–54	141,892 women (17, 360 women used levonorgestrel-releasing intrauterine systems and 165 cases)	no difference between system users and average Finnish female population in any of the 5-year age groups (only p-values reported, and not effect estimates)	no association between length of time elapsed from system insertion up to 10 years in any age group	Very low (observational study, imprecision, risk of bias§)

*Authors note that heterogeneity of location is a limitation because different formulations are more common in different countries (eg, discontinuous cyclic administration [standard in France] vs. continuous daily [standard in United States]) and European counties have access to additional progestin-only pills not sold in the united states (eg, desogestrel)

† Indirectness downgrade assigned because progestin-only pills evaluated as a class, but different progestins may have different effects. Additionally, most included studies were conducted before the year 2000, and numerous formulations of progestin have emerged since then, so the findings may not represent current risk of progestin on breast cancer.

‡ Authors reported that differences in formulations used may account for lack of replication of this result in other studies included in review.

§ Risk of bias downgrade assigned based on case control study design (see 'Other considerations' bullets below for further detail).

- Other considerations:
    - Two additional studies evaluating progestin-only formulation exposure and breast cancer risk that appeared to meet Samson 2016 eligibility criteria but that were not among the 6 studies included in Samson 2016 were identified: Soini 2014 (identified through Discussion section of Mørch 2017) and Dinger 2011 (identified through Discussion section of Soini 2014). In addition, the reporting of Backman 2005 in Samson 2016 SR was incomplete, preventing an adequate assessment of its certainty. Therefore, we obtained full-text for these three studies all of which evaluated levonorgestrel-releasing intrauterine system as

the progestin-only formulation. Soini 2014 was a robust nationwide cohort study with adjustment for key confounding variables which found an increased risk of breast cancer with levonorgestrel-releasing intrauterine system which we considered Low certainty evidence. Backman 2005 and Dinger 2011 were both found to have flaws that dropped them to Very low certainty. We have not prepared full summaries for Backman 2005 and Dinger 2011, and instead we have briefly summarized below why we consider these two studies to have Very low certainty evidence (and hence not progressed to Synthesis):

- Backman 2005
  - Upon review of full text, we found key potential confounding factors (including genetic background, reproductive and hormonal factors, factors related to life-style, environmental factors [such as smoking and alcohol use and geographic location], various factors related to socioeconomic status, and education) were not controlled for; we therefore added an additional downgrade for risk of bias.
- Dinger 2011
  - Upon review of full text, we found that this population-based case-control study was at a risk for recall bias for prognostic factors; we therefore added an additional downgrade for risk of bias.

- None of the six studies included in the Samson 2016 SR that evaluated the following progestin-only formulations were progressed to Synthesis section for reasons described below
  - levonorgestrel-releasing intrauterine system
    - Backman 2005 and Dinger 2011 – reasons described in bullets directly above
  - oral progestin – not further defined
    - Marchbanks 2002, Fabre 2007, and Kumle 2002
    - because oral progestin was not further defined in these 3 studies and because Mørch 2017 suggests there may be increased risk in only some progestin-only formulations (eg, levonorgestrel) and not others (eg, norethisterone), a combined measure may not be appropriate and these three studies were therefore additionally downgraded for indirectness
  - injections
    - Strom 2004 (evaluated injections and implants) and Shapiro 2000
    - both studies were case-control (not population-based) and therefore at increased risk of other sources of bias (eg, recall bias) compared to the national cohort study (Mørch 2017)
  - implant
    - Strom 2004 (evaluated injections and implants)
    - case-control study (as noted above) and considered inferior in study design to Mørch 2017 nationwide cohort study
- Because the limitations of the 6 studies included in Mørch 2017, outcomes from only Mørch 2017 were used for combined oral contraceptive products and for all progestin-only products except levonorgestrel-releasing intrauterine system for which data from Soini 2014 were also used

SOINI 2014
Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Pukkala E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol. 2014 Aug;124(2 Pt 1):292-9. PubMed

Relevant to FAQ4

- **Study design:** observational study
  - national cohort study in Finland, 1994 to 2007
  - incidence of cancers in users of levonorgestrel-releasing intrauterine system was compared with incidence in general population using analysis of Finnish registry data
    - cancer risk-related potential confounders that were adjusted for included smoking, alcohol consumption, physical activity, diet, and socioeconomic status; the data for these were obtained from other nationwide registries
- **Population:** all women in Finland aged 30–49 years using a levonorgestrel-releasing intrauterine system for treating menorrhagia in 1994 to 2007
- **Intervention:** levonorgestrel-releasing intrauterine system users
- **Comparison:** general population (including also hormonal intrauterine system users and those with previous hysterectomy or salpingo-oophorectomy)

- **Study inclusion criteria:** no additional relevant

- **Number of studies:** not applicable
- **Number of participants:** 93,843
- **Duration of follow-up:** 855,324 women-years (follow-up ended on December 31, 2009 or 55th birthday of patients)

- **Results and certainty:**

Observed and expected numbers of breast cancer cases and standardized incidence ratios (with 95% CIs) among Finnish women who bought the levonorgestrel-releasing intrauterine system during 1994–2007 in those ages 30–49 years*

No. of purchases of levonorgestrel-releasing	Observed	Expected	Standardized Incidence Ratio	95% CI	Observed–Expected	Certainty (downgrade)

intrauterine system						
≥ 1†	1,542	1,292.2	1.19	1.13 to 1.25	250	Low (cohort design)
≥ 2‡	271	193.2	1.40	1.24 to 1.57	78	Low (cohort design)

* Follow-up until age 55 years

† Follow-up started from the first purchase of levonorgestrel-releasing intrauterine system

‡ Follow-up started from the second purchase of levonorgestrel-releasing intrauterine system

TEPPER 2016

Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: A systematic review. Contraception. 2016 Dec;94(6):678-700. PubMed

Relevant to FAQ4

- **Study design:** systematic review of observational studies
- **Population:** review included 20 studies involving women in general population without certain characteristics or medical conditions that put them at increased risk for venous thromboembolism or arterial thromboembolism (the latter of which was defined to include stroke and acute myocardial infarction) or who were not specified to have such characteristics/medical conditions
    - review also included 9 studies which examined women with such characteristics/medical conditions associated with thrombosis risk (analyzed separately) but we restricted to the subset of studies of women without such characteristics/medical conditions
- **Intervention:** all progestin-only pills, injectables, implants, and levonorgestrel-releasing intrauterine system
- **Comparison:** nonhormonal contraceptives or no contraceptive method
- **Study inclusion criteria:**
    - reported one of following 3 outcomes of interest: venous thromboembolism, stroke, or acute myocardial infarction
        - 20 studies examined women in general population, but we restricted to the 11 studies (from 13 publications) that reported *risk of venous thromboembolism* among women in general population (Table 2 and Fig 5)
    - published through January 2016
- **Number of studies:** 11 studies examined women in general population and reported risk of venous thromboembolism
- **Number of participants:** summed number not reported
- **Duration of follow-up:** not reported

- **Results:**

Risk of venous thromboembolism (VTE) among women in general population using progestin-only contraceptives vs. nonusers, by type of progestin-only product (no pooled estimate reported for any of the following)

Agent	No. relevant analyses/studies	Key findings	Certainty (reason for downgrade)
depot medroxyprogesterone acetate (DMPA)	3	▪ two case-control studies found significantly increased odds of VTE among women using DMPA vs. nonusers ○ OR 3.0 (95% CI 1.2 to 7.5) in 1 study – diagnosed from "anticoagulation clinic" ○ OR 2.2 (95% CI 1.3 to 4.0) in 1 study – diagnosed from "medical records and imaging"; only included if started anticoagulation ▪ similar magnitude of risk that was not statistically significant (OR 2.2, 95% CI 0.7 to 7.3) in 1 case-control study – diagnosis verified by "medical records and imaging"	Very low certainty of increase in VTE with DMPA with downgrade for observational study design and additional downgrade for case-control study design (higher risk of bias)
implants	1	▪ 1 nationwide registry cohort study showed no significant difference in VTEs with use of implants in analysis limited to *confirmed* VTEs (rate ratio 1.4, 95% CI 0.6 to 3.4; these were the results reported in Fig 5 forest plot) but showed significant increase in analysis including *all* VTEs (rate ratio 2.1, 95% CI 1.3 to 3.5; these additional results reported in Results text) • 1 other study showed no significant difference in VTEs in population with use of implants and desogestrel POPs combined ○ Fig 5 forest plot indicated point estimate slightly favored decreased risk of VTE with intervention; effect estimate in Table 2 is OR 0.9 (95% CI 0.5 to 1.6) ○ because the population included both women with implants and women with desogestrel POPs, this study cannot directly address effects of implants specifically	Very low certainty of increase in VTE with implant (based on assessment of implants only study, as noted above) with downgrades for observational study design and inconsistency (significant increase found only when outcome operationalized as all VTEs)

		and is mentioned here only for completeness	
levonorgestrel-releasing intrauterine system	5	▪ none of 5 studies (including ≥ 1 nationwide registry cohort study) found increased odds of VTE among women using levonorgestrel-releasing intrauterine system vs. nonusers ○ point estimate favored decreased risk of VTE in all 5 studies, with OR ranging from 0.3 to 0.9 ○ highest upper bound of 95% CI was OR of 1.3 ○ includes relevant results from Lidegaard 2009 (summarized separately in this document)	Low certainty of no important increase in VTE with levonorgestrel-releasing intrauterine system with downgrade for observational study designs
progestin-only pills (POPs)	10 relevant analyses from 8 studies	▪ overall ○ no significant difference in 9 analyses/7 studies (including > 1 nationwide registry cohort study) of use of POPs for contraceptive purposes (point estimates of 4 favored increased risk and points estimates of 5 favored decreased risk, and with at least 2 included studies having non-overlapping CIs) ▪ includes relevant results from Lidegaard 2009 (Danish national registry based cohort study, summarized separately in this document) ○ significant increase (OR 5.9, 95% CI 1.2 to 30.1) in 1 analysis/study of women using POPs for therapeutic indications ▪ conditions being treated were not stated ▪ formulations and doses of POPs were not reported ▪ specific POPs evaluated - in addition to Lidegaard 2009 (included in Fig 5, but not included below because already summarized separately, and which reported Very low evidence of no important difference in venous thrombosis for women using the specific progestin-only oral pills levonorgestrel or norethisterone and desogestrel [with non-users as reference standard] [with imprecision downgrade for both options]), one other study in Fig 5	*Overall* Very low certainty of no increase in VTE with POP with downgrades for observational study design and inconsistency *For specific POPs* Very low certainty of no important increase in VTE with POP with desogestrel with downgrades for observational study design and imprecision Very low certainty of no important increase in VTE with POP with norethisterone with downgrades for observational study design and imprecision

		(Lidegaard 2011 – also a Danish national registry based cohort study) also reported results separately for two specific progestogens included in POP as described below ○ no significant difference with POP with desogestrel with point estimate favoring decreased risk of VTE: 0.6 (95% CI 0.3 to 1.4) ○ no significant difference with POP with norethisterone with point estimate favoring decreased risk of VTE: 0.6 (95% CI 0.3 to 1.1)	

- **Other considerations**
  - Our systematic review search (2nd-round searching) identified an earlier systematic review (Bergendal 2009) that also evaluated progestogen-only contraception and risks of VTE and included 5 studies, all 5 of which are included in Tepper 2016.

Evidence report for hormonal treatment of endometriosis

Reference list

Prepared by EBSCO Information Services

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Prepared by EBSCO Health Innovations and EBM Development Department:

Brian S. Alper, MD, MSPH, FAAFP, Vice President

Martin Mayer, DMSc, MS, PA-C, Clinical Evidence Synthesizer

Eric Manheimer, PhD, EBM Editor

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