Premenstrual syndrome

Search date April 2014

Irene Kwan and Joseph Loze Onwude

ABSTRACT

INTRODUCTION: A woman has premenstrual syndrome (PMS) if she complains of recurrent psychological and/or physical symptoms occurring during the luteal phase of the menstrual cycle, and often resolving by the end of menstruation. Symptom severity can vary between women. Premenstrual symptoms occur in 95% of women of reproductive age. Severe, debilitating symptoms occur in about 5% of those women. There is no consensus on how symptom severity should be assessed for PMS, which has led to the use of a wide variety of symptom scores and scales, thus making it difficult to synthesise data on treatment efficacy. The cyclical nature of the condition also makes it difficult to conduct RCTs. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of continuous hormonal treatments in women with premenstrual syndrome? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 132 studies. After deduplication and removal of conference abstracts, 132 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 102 studies and the further review of 30 full publications. Of the 30 full articles evaluated, one systematic review and three RCTs were added to this overview. We performed a GRADE evaluation for three PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for three interventions based on information relating to the effectiveness and safety of continuous combined oral contraceptives, continuous transdermal estradiol, and continuous subcutaneous estradiol implants.

QUESTIONS

What are the effects of continuous hormonal treatments in women with premenstrual syndrome?. 4

INTERVENTIONS

CONTINUOUS HORMONAL TREATMENTS

Unknown effectiveness

Continuous combined oral contraceptives (with no break in treatment) New 4

Continuous transdermal estradiol (with no break in treatment) in women with an intact uterus New . . . 6

Continuous transdermal estradiol (with no break in treatment) in women with hysterectomy but no bilateral salpingo-oophorectomy New 8

Continuous subcutaneous estradiol implant (with no break in treatment) in women with an intact uterus New 8

Continuous subcutaneous estradiol implant (with no break in treatment) in women with a hysterectomy but no bilateral salpingo-oophorectomy New 11

Covered elsewhere in Clinical Evidence

Breast pain

Key points

- A woman has premenstrual syndrome (PMS) if she complains of recurrent psychological and/or physical symptoms occurring during the luteal phase of the menstrual cycle, and often resolving by the end of menstruation. Symptom severity can vary between women.

  Psychological symptoms of PMS include irritability, depression, crying/tearfulness, and anxiety. Physical symptoms of PMS include abdominal bloating, breast tenderness, and headaches.

  Premenstrual symptoms occur in 95% of all women of reproductive age. Severe, debilitating symptoms occur in about 5% of those women.

  The cyclical nature of PMS makes it difficult to conduct RCTs. Furthermore, the lack of consensus on how premenstrual symptom severity should be assessed has meant that RCTs use different symptom scores and scales, which makes it difficult to synthesise data.

  There is little good quality evidence for any of the wide range of treatments available for PMS, and the selection of treatment is mainly governed by personal choice. The clinician plays a key role in facilitating this choice, and in reassuring women with PMS without coexisting gynaecological problems that there is nothing seriously wrong.

- We don't know whether continuous daily oral levonorgestrel plus ethinylestradiol is more effective than placebo at improving premenstrual symptoms because we only found one trial and this specifically studied women with premenstrual dysphoric disorder.

  We found no evidence in women with PMS who did not have premenstrual dysphoric disorder.

  Adverse effects that may occur with continuous daily oral levonorgestrel plus ethinylestradiol include vaginal haemorrhage, metrorrhagia, and flu-like symptoms. There is also a concern that the combined contraceptive pill is associated with more serious adverse events, such as deep vein thrombosis (DVT), breast cancer, pulmonary embolism, and stroke.

- We found insufficient evidence (only one RCT with small numbers) to judge the effectiveness of continuous transdermal estradiol plus cyclical oral norethisterone for treating PMS in women with an intact uterus.

© BMJ Publishing Group Ltd 2015. All rights reserved.

- Continuous subcutaneous estradiol implant plus cyclical norethisterone may be more effective than placebo at improving premenstrual symptoms in women with an intact uterus, but this is based on one RCT.
- We found no RCTs on the effectiveness of continuous transdermal estradiol or continuous subcutaneous estradiol implant for treating PMS in women who had had a hysterectomy without bilateral salpingo-oophorectomy.

Clinical context

GENERAL BACKGROUND

Premenstrual symptoms are common, occurring in 95% of women of reproductive age. A woman has premenstrual syndrome (PMS) if she complains of recurrent psychological and/or physical symptoms occurring during the luteal phase of the menstrual cycle, and often resolving by the end of menstruation. Symptom severity can vary between women. At the extreme severe end of the spectrum, PMS can present as premenstrual dysphoric disorder.

FOCUS OF THE REVIEW

This evidence overview aims to identify effective treatments for managing PMS, with minimum adverse effects. There are many different types of treatment that have been used. For this update, we have focused on investigating the evidence for hormonal treatments, as these are interventions that are probably more acceptable to women compared with other options.

COMMENTS ON EVIDENCE

Surprisingly for such a common condition, there have been very few RCTs comparing different hormonal interventions. Therefore, it is difficult to draw firm conclusions. The cyclical nature of PMS makes it difficult to conduct RCTs. Furthermore, the lack of consensus on how premenstrual symptom severity should be assessed has meant that RCTs use different symptom scores and scales, which makes it difficult to synthesise data. Confidence in the findings of the trials that have been done may be increased if these trials are repeated.

SEARCH AND APPRAISAL SUMMARY

The literature search was carried out in April 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 132 studies. After deduplication and removal of conference abstracts, 132 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 102 studies and the further review of 30 full publications. Of the 30 full articles evaluated, one systematic review and three RCTs were added at this update.

ADDITIONAL INFORMATION

There is a need for further high-quality trials in this field as the current available evidence is limited.

DEFINITION	A woman has premenstrual syndrome (PMS) if she complains of recurrent psychological and/or physical symptoms occurring specifically during the luteal phase of the menstrual cycle, and often resolving by the end of menstruation. [1] The symptoms can also persist during the bleeding phase (for details of psychological, behavioural, and physical symptoms commonly reported in women with PMS, see table 1, p 13). **Severe premenstrual syndrome** The definition of severe PMS varies among RCTs, but in recent studies standardised criteria have been used to diagnose one variant of severe PMS — premenstrual dysphoric disorder (PMDD). The criteria are based on at least five symptoms, including one of four core psychological symptoms (from a list of 17 physical and psychological symptoms) and being severe before menstruation starts and mild or absent after menstruation. [2] [3] The 17 symptoms are depression, feeling hopeless or guilty, anxiety/tension, mood swings, irritability/persistent anger, decreased interest, poor concentration, fatigue, food craving or increased appetite, sleep disturbance, feeling out of control or overwhelmed, poor coordination, headache, aches, swelling/bloating/weight gain, cramps, and breast tenderness.
INCIDENCE/ PREVALENCE	Premenstrual symptoms occur in 95% of all women of reproductive age; severe, debilitating symptoms occur in about 5% of those women. [1]
AETIOLOGY/ RISK FACTORS	The cause is unknown but hormonal and other factors (possibly neuroendocrine) probably contribute. [4] [5]
PROGNOSIS	Symptoms of PMS can recur after treatment is stopped, except after oophorectomy and menopause.

© BMJ Publishing Group Ltd 2015. All rights reserved.

AIMS OF INTERVENTION To improve or eliminate physical and psychological symptoms with minimal adverse effects; and to minimise the impact on normal functioning, interpersonal relationships, and quality of life.

OUTCOMES **Premenstrual symptoms** There is no consensus on how premenstrual symptom severity should be assessed. One review of PMS outcomes found 65 different questionnaires or scales, measuring 199 different symptoms or signs. [6] **Adverse effects**.

METHODS **Search strategy** *BMJ Clinical Evidence* search and appraisal April 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to April 2014, Embase 1980 to April 2014, and The Cochrane Database of Systematic Reviews 2014, issue 2 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing more than 20 individuals. For continuous combined oral contraceptives, and continuous transdermal estradiol, we only included RCTs with minimum treatment duration of 3 months. For continuous subcutaneous estradiol implants, we only included RCTs with minimum treatment duration of 6 months. There was no minimum length of follow-up. Many of the RCTs we retrieved had problems with retaining participants throughout follow-up; this may be because of the cyclical nature of PMS. We, therefore, did not exclude RCTs on the basis of high withdrawal rates or high loss to follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included systematic reviews and subsequent RCTs that: (1) diagnosed PMS by validated scales before randomisation; (2) used a pre-randomisation placebo cycle to exclude women with a non-specific response; and (3) contained sufficient cycles to allow for symptom variability between cycles. Few trials fulfilled these criteria. The wide range of diagnostic scales, outcome criteria, and dosing schedules made comparison between trials difficult. We excluded reviews that systematically searched electronic databases but did not use overt criteria to appraise the results. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions: What are the effects of drug treatments in women with premenstrual syndrome? What are the effects of hormonal treatments in women with premenstrual syndrome? What are the effects of psychological interventions in women with premenstrual syndrome? What are the effects of physical therapy in women with premenstrual syndrome? What are the effects of dietary supplements in women with premenstrual syndrome? What are the effects of surgical treatments in women with premenstrual syndrome? from this overview. We have added the following question: What are the effects of continuous hormonal treatments in women with premenstrual syndrome? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue which may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined pop-

© BMJ Publishing Group Ltd 2015. All rights reserved.

ulations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of continuous hormonal treatments in women with premenstrual syndrome?**

OPTION **CONTINUOUS COMBINED ORAL CONTRACEPTIVES (WITH NO BREAK IN TREATMENT)**
N e w

- For GRADE evaluation of interventions for Premenstrual syndrome, see table, p 13 .
- We don't know whether continuous daily oral levonorgestrel plus ethinylestradiol is more effective than placebo at improving premenstrual symptoms because we only found one RCT, and it specifically studied women with premenstrual dysphoric disorder (PMDD).
- The findings in women with PMDD may not be directly applicable to women with less severe PMS symptoms. We found no studies in women with PMS who did not have PMDD.
- There may be more adverse effects associated with continuous daily oral levonorgestrel plus ethinylestradiol compared with placebo, such as vaginal haemorrhage, metrorrhagia, and flu-like symptoms.
- In the only RCT we found, the combined oral contraceptive pill used was levonorgestrel 90 micrograms combined with ethinylestradiol 20 micrograms; the latter was a low-dose ethinylestradiol to minimise adverse effects. However, it is important to note that venous thromboembolism, pulmonary embolism, and strokes can also occur with the use of low-dose combined oral contraceptives.

Benefits and harms

Continuous combined oral contraceptives (with no break in treatment) versus placebo:

We found one systematic review (search date 2011) [7] and one subsequent RCT. [8] The review found no relevant RCTs. The subsequent RCT (386 women with premenstrual dysphoric disorder) compared continuous low-dose combined pill containing levonorgestrel plus ethinylestradiol with matching placebo for 112 days (4 consecutive 28-day pill packs). Premenstrual symptoms were assessed using a symptom questionnaire. Although the RCT reported results for four treatment cycles, it designated the first treatment cycle as a primary endpoint because of potentially different menstrual bleeding patterns between groups, which could jeopardise blinding (see Further information on studies). [8]

Premenstrual symptoms

Continuous combined oral contraceptives compared with placebo We don't know whether continuous combined pill containing levonorgestrel plus ethinylestradiol is more effective than placebo at improving premenstrual symptom scores (measured by the Daily Record of Severity of Problems [DRSP] questionnaire) in women with premenstrual dysphoric disorder (PMDD) following 3 months of treatment. We found no RCTs in women with PMS who did not have PMDD (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Premenstrual symptoms					
[8] RCT	386 women, aged 18–49 years, with premenstrual dysphoric disorder meeting DSM-IV-TR criteria	**Mean change from baseline in total DRSP score , late luteal phase for the third treatment cycle** with levonorgestrel plus ethinylestradiol with placebo Absolute results reported graphically	Reported as not significant P value not provided Results based on 265/386 (69%) women initially randomised See Further information on studies	⟷	Not significant

Adverse effects

© BMJ Publishing Group Ltd 2015. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[8] RCT	386 women, aged 18–49 years, with premenstrual dysphoric disorder meeting DSM-IV-TR criteria	**Any treatment-emergent adverse effect** 130/186 (70%) with levonorgestrel plus ethinylestradiol 108/181 (60%) with placebo	P = 0.049	○○○	placebo
[8] RCT	386 women, aged 18–49 years, with premenstrual dysphoric disorder meeting DSM-IV-TR criteria	**Metrorrhagia** 17/186 (9%) with levonorgestrel plus ethinylestradiol 2/181 (1%) with placebo	P <0.001	○○○	placebo
[8] RCT	386 women, aged 18–49 years, with premenstrual dysphoric disorder meeting DSM-IV-TR criteria	**Flu syndrome** 9/186 (5%) with levonorgestrel plus ethinylestradiol 0/181 (0%) with placebo	P <0.005	○○○	placebo
[8] RCT	386 women, aged 18–49 years, with premenstrual dysphoric disorder meeting DSM-IV-TR criteria	**Menorrhagia** 9/186 (5%) with levonorgestrel plus ethinylestradiol 0/181 (0%) with placebo	P <0.005	○○○	placebo
[8] RCT	386 women, aged 18–49 years, with premenstrual dysphoric disorder meeting DSM-IV-TR criteria	**Vaginal haemorrhage** 8/186 (4%) with levonorgestrel plus ethinylestradiol 0/181 (0%) with placebo	P <0.01	○○○	placebo
[8] RCT	386 women, aged 18–49 years, with premenstrual dysphoric disorder meeting DSM-IV-TR criteria	**Study discontinuation due to an adverse event** 24 women with levonorgestrel plus ethinylestradiol 6 women with placebo The most common causes were vaginal haemorrhage (5 women), menstrual disorder (4 women), menorrhagia (3 women), and hypertension (2 women)	P <0.001	○○○	placebo
[8] RCT	386 women, aged 18–49 years, with premenstrual dysphoric disorder meeting DSM-IV-TR criteria	**Serious adverse effects** with levonorgestrel plus ethinylestradiol with placebo Absolute results not reported 2 women receiving continuous levonorgestrel plus ethinylestradiol, and 3 women receiving placebo, had serious adverse effects. 1 woman taking placebo developed breast cancer; 1 woman on levonorgestrel plus ethinylestradiol had a deep vein thrombosis, while another woman had a pulmonary embolism (both withdrawn from the study)			

© BMJ Publishing Group Ltd 2015. All rights reserved.

Continuous combined oral contraceptives (with no break in treatment) versus cyclical combined oral contraceptives (with a break period each month):

We found no systematic review or RCTs.

Further information on studies

[8] We have preferentially reported results at 3 months, which is our minimum treatment period, at which point the RCT found no significant difference between groups. The RCT found a significant difference in favour of levonorgestrel plus ethinylestradiol at 1 month (mean change in DRSP score late luteal phase, 328/386 [84%] of women randomised, P <0.001) and 2 months (mean change in DRSP score late luteal phase, 291/386 [75%] of women randomised, P <0.05). However, the statistical analysis was based on mean scores, whereas the DRSP measure used was an ordinal measure (6-point severity scale), thus making the results difficult to interpret.

[8] The RCT measured premenstrual symptoms using the DRSP score, which collected 21 emotional and physical items within 11 domains of the DSM-IV-TR criteria, and three items assessing functional impairment. Items were rated on a six-point severity scale (degree of problems experienced from 1 [not at all] to 6 [extreme]).

[8] There was an increasing drop-out over the four cycles that the RCT reported, and DRSP results were based on 84% (328/386) of women randomised at cycle one, 75% (291/386) of women at cycle two, 69% (265/386) of women at cycle three, and 41% (158/386) of women at cycle four. The RCT did not report an ITT analysis. The RCT declared that some of the authors were employed by a pharmaceutical company.

Comment: In this option, we have only considered RCTs with minimum treatment duration of 3 months.

Clinical comment on the evidence

Generally, the combined pill describes an oestrogen and a progestogen for 21 days and either an inactive pill or a break for 7 days. When the combined pill is used continuously, this describes using the combined pill without the pill break. This RCT [8] used a continuous combined contraceptive pill, with 112 days of both 20 micrograms ethinylestradiol and 90 micrograms of levonorgrestrel.

The concept of using the combined pill to minimise the symptoms and restrictions of PMS is not new, but using continuous combined contraceptive pills for 3 to 6 months is fairly novel. Although this appears to work clinically, there is still concern that the low-dose continuous combined contraceptive pill is still associated with serious adverse events, such as deep vein thrombosis (DVT), pulmonary embolism, and stroke.

One aim of the RCT was to assess if this low-dose continuous combined oral contraceptive would be safer than the standard combined oral contraceptive. The results showed that there were still adverse effects with this low-dose continuous combined treatment and also adverse effects in the placebo group. Moreover, the menstrual abnormalities and vaginal bleeding are known to be associated with the low-dose combined pill, and rarely with the full dose. The standard-dose combined pills are used to treat menorrhagia and metrorrhagia. Some cervical bleeding from erosion of the cervix can occur with the standard-dose treatment, but this concern is usually minimal if discussed prior to start of treatment.

OPTION CONTINUOUS TRANSDERMAL ESTRADIOL (WITH NO BREAK IN TREATMENT) IN WOMEN WITH AN INTACT UTERUS New

- For GRADE evaluation of interventions for Premenstrual syndrome, see table, p 13 .
- We found only one RCT, making it difficult to be confident on the effectiveness of continuous transdermal estradiol for treating premenstrual symptoms in women with an intact uterus.
- In the one RCT we found comparing continuous transdermal estradiol with placebo, oral norethisterone was added from day 19 to 26 of each cycle in both groups to ensure endometrial protection in the active treatment group and regular bleed in both groups.

© BMJ Publishing Group Ltd 2015. All rights reserved.

Benefits and harms

Continuous transdermal estradiol (with no break in treatment) versus placebo in women with an intact uterus:

We found one crossover double-blind RCT (40 women with premenstrual symptoms and an intact uterus), which compared estradiol patches with placebo patches over 6 months with crossover at 3 months. Oral norethisterone was added from day 19 to 26 of each cycle in both groups to ensure endometrial protection in the active treatment group and regular bleed in both groups (see Further information on studies). [9]

Premenstrual symptoms

Continuous transdermal estradiol (with no break in treatment) compared with placebo We don't know how estradiol patches and placebo compare at improving premenstrual symptoms (as measured by the MDQ and PDQ questionnaire) following 3 months of treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Premenstrual symptoms					
[9] RCT **Crossover design**	40 women with premenstrual symptoms and an intact uterus	**Symptom cluster scores (assessed by the Moos Menstrual Distress Questionnaire [MDQ] and the Premenstrual Distress Questionnaire [PDQ])** with estradiol patches with placebo Absolute results reported graphically Analysis of 20 women in each group	The RCT reported a within-group analysis (baseline comparison; between-group significance not assessed as not appropriate for this type of study) The RCT reported that at 3 months, both the active treatment and placebo groups showed improvement in symptom cluster scores; however, after crossover at 3 months, it noted that, in women switching from the active group to placebo, there was a tendency for scores to deteriorate, while in women switching from placebo to active treatment, there was a tendency for scores to keep improving		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[9] RCT **Crossover design**	40 women with premenstrual symptoms and an intact uterus	**Adverse effects** with estradiol patches with placebo The RCT reported that 12 women noticed skin irritation, 10 women were left with some skin pigmentation at the site of application of the patch, and 4 women (2 in each group) had skin reactions within the first month of starting treatment			

Continuous transdermal estradiol (with no break in treatment) versus cyclical transdermal estradiol (with a break period each month) in women with an intact uterus:

We found no systematic review or RCTs.

© BMJ Publishing Group Ltd 2015. All rights reserved.

Further information on studies

[9] The RCT compared estradiol patches changed every 3 days versus placebo patches over 6 months, with crossover at 3 months. It was unclear if there was a wash-out period before crossover. Even though this is a small study, it is important to consider as it is the only one we found studying this intervention for women with PMS.

Comment: In this option, we have only considered RCTs with minimum treatment duration of 3 months.

Clinical guide
Continuous transdermal estradiol patches should minimise the symptoms of PMS that are linked to lower estradiol levels of the luteal phase of the menstrual cycle. They should be combined with cyclical progestogen to protect the uterus in women with an intact uterus. This protection is not required in women without a uterus.

OPTION CONTINUOUS TRANSDERMAL ESTRADIOL (WITH NO BREAK IN TREATMENT) IN WOMEN WITH HYSTERECTOMY BUT NO BILATERAL SALPINGO-OOPHORECTOMY New

- For GRADE evaluation of interventions for Premenstrual syndrome, see table, p 13 .
- We found no evidence to judge the effectiveness of continuous transdermal estradiol for treating premenstrual symptoms in women with hysterectomy but no bilateral salpingo-oophorectomy.

Benefits and harms

Continuous transdermal estradiol (with no break in treatment) versus placebo in women with a hysterectomy but no bilateral salpingo-oophorectomy:

We found no systematic review or RCTs.

Continuous transdermal estradiol (with no break in treatment) versus cyclical transdermal estradiol (with a break period each month) in women with a hysterectomy but no bilateral salpingo-oophorectomy:

We found no systematic review or RCTs.

Comment: In this option, we have only considered RCTs with minimum treatment duration of 3 months.

Clinical guide
Continuous transdermal estradiol patches should minimise the symptoms of PMS that are linked to lower estradiol levels of the luteal phase of the menstrual cycle. Uterine protection is not required in women who have had a hysterectomy.

OPTION CONTINUOUS SUBCUTANEOUS ESTRADIOL IMPLANT (WITH NO BREAK IN TREATMENT) IN WOMEN WITH AN INTACT UTERUS New

- For GRADE evaluation of interventions for Premenstrual syndrome, see table, p 13 .
- Continuous subcutaneous estradiol implant plus cyclical norethisterone may be more effective than placebo at improving symptoms in women with PMS and an intact uterus; however, this is based on evidence from one RCT.

Benefits and harms

Continuous subcutaneous estradiol implant (with no break in treatment) versus placebo in women with an intact uterus:

We found one double-blind RCT (68 women with an intact uterus), which compared subcutaneous estradiol implant plus oral norethisterone for 7 days per cycle with placebo implant plus oral placebo, identical in appearance with

© BMJ Publishing Group Ltd 2015. All rights reserved.

norethisterone. [10] The RCT assessed daily premenstrual symptoms using a modified Moos Menstrual Distress Questionnaire (34 adverse symptoms in 6 symptom clusters, scored 0 [no symptoms] to 3 [severe symptoms]), how well participants were feeling using a visual analogue scale (VAS, 100 mm), and current psychiatric morbidity using the 60-item general health questionnaire.

Premenstrual symptoms

Continuous subcutaneous estradiol implant compared with placebo Continuous subcutaneous estradiol implant plus cyclical oral norethisterone may be more effective than placebo implant plus oral placebo at improving daily premenstrual symptom scores (measured by the modified Moos Menstrual Distress Questionnaire) at up to 6 months in women with PMS and an intact uterus, but we don't know about general improvement (measured by VAS scores) or psychiatric morbidity (measured by the general health questionnaire) (very-low quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Premenstrual symptoms					
[10] RCT	68 women, aged 25–45 years with regular periods, premenstrual distress for at least 6 months, diagnosis confirmed by prospective daily symptom rating assessment	**Mean improvement in daily total Menstrual Distress Questionnaire scores , from 0–2 months** 0.252 with subcutaneous estradiol implant plus oral norethisterone 0.115 with placebo implant plus oral placebo Results based on 60/68 (88%) women randomised	Reported as P <0.2 Further details not reported	⟷	Not significant
[10] RCT	68 women, aged 25–45 years with regular periods, premenstrual distress for at least 6 months, diagnosis confirmed by prospective daily symptom rating assessment	**Mean improvement in daily total Menstrual Distress Questionnaire scores , from 0–4 months** 0.206 with subcutaneous estradiol implant plus oral norethisterone 0.035 with placebo implant plus oral placebo Results based on 48/68 (71%) women randomised	P <0.02	○○○	subcutaneous estradiol implant plus oral norethisterone
[10] RCT	68 women, aged 25–45 years with regular periods, premenstrual distress for at least 6 months, diagnosis confirmed by prospective daily symptom rating assessment	**Mean improvement in daily total Menstrual Distress Questionnaire scores , from 0–6 months** +0.236 with subcutaneous estradiol implant plus oral norethisterone –0.030 with placebo implant plus oral placebo Results based on 24/68 (35%) women randomised	P <0.01 Results were also significant at 0–8 months, and 0–10 months, but based on increasingly fewer participants (see Further information on studies)	○○○	subcutaneous estradiol implant plus oral norethisterone
[10] RCT	68 women, aged 25–45 years with regular periods, premenstrual distress for at least 6 months, diagnosis confirmed by prospective daily symptom rating assessment	**Mean improvement in visual analogue scale score (from 0 = very well to 100 = very unwell) , from 0–6 months** 40.2 with subcutaneous estradiol implant plus oral norethisterone 37.6 with placebo implant plus oral placebo Results based on 27/68 (40%) women randomised	P >0.1	⟷	Not significant
[10] RCT	68 women, aged 25–45 years with regular periods, premenstrual distress for at least 6 months, diagnosis confirmed by prospective daily	**Mean improvement in general health questionnaire scores (score obtained by counting number of items for which morbidity increasing) , from 0–6 months** 5.3 with subcutaneous estradiol implant plus oral norethisterone	P >0.1	⟷	Not significant

© BMJ Publishing Group Ltd 2015. All rights reserved.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	symptom rating assessment	5.8 with placebo implant plus oral placebo Results based on 27/68 (40%) women randomised			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] RCT	68 women, aged 25–45 years with regular periods, premenstrual distress for at least 6 months, diagnosis confirmed by prospective daily symptom rating assessment	**Adverse effects** with subcutaneous estradiol implant plus oral norethisterone with placebo implant plus oral placebo The RCT reported that adverse effects were mild and infrequent; the most common adverse effects were mastalgia (9 cases with estradiol *v* 2 cases with placebo), nausea (3 with estradiol *v* 4 with placebo), weight gain (5 with estradiol *v* 0 with placebo), and headache (2 with estradiol *v* 3 with placebo)	Significance not reported		

Continuous subcutaneous estradiol implant (with no break in treatment) versus cyclical transdermal estradiol (with a break period each month) in women with an intact uterus:

We found no systematic review or RCTs.

Continuous subcutaneous estradiol implant (with no break in treatment) versus cyclical combined oral contraceptives (with a break period each month) in women with an intact uterus:

We found no systematic review or RCTs.

Further information on studies

[10] The RCT noted a large response to placebo, and all but 2 of 35 women receiving the placebo implant reported improvement during the first 3 months. This large initial effect tailed off by 6 months, and the RCT speculated that this initial high response might be due to the 'surgical' nature of the intervention, as well as other factors.

[10] With regard to improvements in total menstrual distress scores, the RCT also found a significant improvement in the estradiol group compared with placebo at 8 and 10 months, although the results were based on increasingly fewer participants (0 to 8 months: 17/68 [25%] of women randomised, P <0.01 [between-group]; 0 to 10 months: 14/68 [21%] of women randomised, P <0.01 [between-group]).

Comment: In this option, we have only considered RCTs with minimum treatment duration of 6 months.

© BMJ Publishing Group Ltd 2015. All rights reserved.

Clinical guide
The potential for estradiol implants to prevent symptoms of PMS follows from the ability to provide consistent, physiological levels of estradiol during the proliferative and luteal phases, and avoids fluctuations of hormone levels seen with other methods of delivery. In clinical practice, this effect increases with time, suggesting that the initial response may be a placebo effect. There is still concern that progestogens can cause serious adverse events, such as breast cancer, and that oral oestrogens can cause deep vein thrombosis (DVT), pulmonary embolism, and strokes. However, in its long history of use since 1947 in menopausal women who are more predisposed to these events, these adverse events have not been associated directly with estradiol implants. With regard to PMS, the population receiving treatment with estradiol implants are younger menstrual women. Current thinking is that adverse events such as breast cancer may be related to the oral progestogen component of combined hormone treatments. In this case, additional Mirena coil that supplies progestogen directly into the uterus where it is needed might be preferable.

OPTION CONTINUOUS SUBCUTANEOUS ESTRADIOL IMPLANT (WITH NO BREAK IN TREATMENT) IN WOMEN WITH A HYSTERECTOMY BUT NO BILATERAL SALPINGO-OOPHORECTOMY

N e w

- For GRADE evaluation of interventions for Premenstrual syndrome, see table, p 13 .
- We found no evidence on the effectiveness of continuous subcutaneous estradiol implant for treating premenstrual symptoms in women with hysterectomy but no bilateral salpingo-oophorectomy.

Benefits and harms

Continuous subcutaneous estradiol implant (with no break in treatment) versus placebo in women with a hysterectomy but no bilateral salpingo-oophorectomy:

We found no systematic review or RCTs.

Continuous subcutaneous estradiol implant (with no break in treatment) versus cyclical transdermal estradiol (with a break period each month) in women with a hysterectomy but no bilateral salpingo-oophorectomy:

We found no systematic review or RCTs.

Continuous subcutaneous estradiol implant (with no break in treatment) versus cyclical combined oral contraceptives (with a break period each month) in women with a hysterectomy but no bilateral salpingo-oophorectomy:

We found no systematic review or RCTs.

Comment: In this option, we have only considered RCTs with minimum treatment duration of 6 months.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Premenstrual dysphoric disorder (PMDD) An intense form of premenstrual syndrome occurring exclusively during the 2 weeks before menses. It often has more psychological symptoms than physical ones. Symptoms may include feelings of hopelessness, anxiety and depression, lethargy, irritability, and low self-esteem.

Salpingo-oophorectomy The removal of the fallopian tube (salpingectomy) and ovary (oophorectomy).

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Continuous combined oral contraceptives (with no break in treatment) New option. One systematic review [7] and one RCT [8] added. Categorised as 'unknown effectiveness'.

© BMJ Publishing Group Ltd 2015. All rights reserved.

Continuous transdermal estradiol (with no break in treatment) in women with an intact uterus New option. One RCT added. [9] Categorised as 'unknown effectiveness'.

Continuous transdermal estradiol (with no break in treatment) in women with a hysterectomy but no bilateral salpingo-oophorectomy New option. Categorised as 'unknown effectiveness'.

Continuous subcutaneous estradiol implant (with no break in treatment) in women with an intact uterus New option. One RCT added. [10] Categorised as 'unknown effectiveness'.

Continuous subcutaneous estradiol implant (with no break in treatment) in women with a hysterectomy but no bilateral salpingo-oophorectomy New option. Categorised as 'unknown effectiveness'.

REFERENCES

1. O'Brien PM. Premenstrual syndrome. London: Blackwell Science, 1987.
2. Steiner M, Romano SJ, Babcock S, et al. The efficacy of fluoxetine in improving physical symptoms associated with premenstrual dysphoric disorder. *Br J Obstet Gynaecol* 2001;108:462–468.[PubMed]
3. Freeman EW, Rickels K, Yonkers KA, et al. Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstet Gynecol* 2001;98:737–744.[PubMed]
4. Rapkin AJ, Morgan M, Goldman L, et al. Progesterone metabolite allopregnanolone in women with premenstrual syndrome. *Obstet Gynecol* 1997;90:709–714.[PubMed]
5. O'Brien PM. Helping women with premenstrual syndrome. *BMJ* 1993;307:1471–1475.[PubMed]
6. Budeiri DJ, Li WP, Dornan JC. Clinical trials of treatments of premenstrual syndrome: entry criteria and scales for measuring treatment outcomes. *Br J Obstet Gynaecol* 1994;101:689–695.[PubMed]
7. Lopez LM, Kaptein A, Helmerhorst FM, et al. Oral contraceptives containing drospirenone for premenstrual syndrome. In: The Cochrane Library, Issue 2, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2011.
8. Halbreich U, Freeman EW, Rapkin AJ, et al. Continuous oral levonorgestrel/ethinyl estradiol for treating premenstrual dysphoric disorder. *Contraception* 2012;85:19–27.[PubMed]
9. Watson NR, Studd JW, Savvas M, et al. Treatment of severe premenstrual syndrome with oestradiol patches and cyclical oral norethisterone. *Lancet* 1989;2:730–732.[PubMed]
10. Magos AL, Brincat M, Studd JW. Treatment of the premenstrual syndrome by subcutaneous estradiol implants and cyclical oral norethisterone: placebo controlled study. *Br Med J (Clin Res Ed)* 1986;292:1629–1633.[PubMed]

Irene Kwan
Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre), Social Science Research Unit (SSRU), UCL Institute of Education
University of London
London
UK

Joseph Loze Onwude
Gynaecologist and Medical Statistician
The Croft
Warley Road
Brentwood
UK

Competing interests: IK and JLO declare that they have no competing interests.
We would like to acknowledge the previous contributors of this chapter, including P. Dimmock, P.M.S. O'Brien, and Katrina Wyatt.

Disclaimer

The information contained in this publication is intended for medical professionals. Categories presented in Clinical Evidence indicate a judgement about the strength of the evidence available to our contributors prior to publication and the relevant importance of benefit and harms. We rely on our contributors to confirm the accuracy of the information presented and to adhere to describe accepted practices. Readers should be aware that professionals in the field may have different opinions. Because of this and regular advances in medical research we strongly recommend that readers' independently verify specified treatments and drugs including manufacturers' guidance. Also, the categories do not indicate whether a particular treatment is generally appropriate or whether it is suitable for a particular individual. Ultimately it is the readers' responsibility to make their own professional judgements, so to appropriately advise and treat their patients. To the fullest extent permitted by law, BMJ Publishing Group Limited and its editors are not responsible for any losses, injury or damage caused to any person or property (including under contract, by negligence, products liability or otherwise) whether they be direct or indirect, special, incidental or consequential, resulting from the application of the information in this publication.

© BMJ Publishing Group Ltd 2015. All rights reserved.

TABLE 1 **Commonly reported symptoms in women with premenstrual syndrome**

Commonly reported symptoms in women with premenstrual syndrome	
Psychological symptoms	Irritability, depression, crying/tearfulness, anxiety, tension, mood swings, lack of concentration, confusion, forgetfulness, unsociableness, restlessness, temper outbursts/anger, sadness/blues, loneliness
Behavioural symptoms	Fatigue, dizziness, sleep/insomnia, decreased efficiency, accident prone, sexual interest changes, increased energy, tiredness
Physical symptoms: pain	Headache/migraine, breast tenderness/soreness/pain/swelling (collectively known as premenstrual mastalgia), back pain, abdominal cramps, general pain
Physical symptoms: bloatedness and swelling	Weight gain, abdominal bloating or swelling, oedema of arms and legs, water retention
Appetite symptoms	Increased appetite, food cravings, nausea

GRADE **Evaluation of interventions for Premenstrual syndrome.**

Important outcomes			Premenstrual symptoms						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of continuous hormonal treatments in women with premenstrual syndrome?									
1 (at least 328) [8]	Premenstrual symptoms	Continuous combined oral contraceptives (with no break in treatment) versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results; directness points deducted for restricted population and high attrition
1 (40) [9]	Premenstrual symptoms	Continuous transdermal estradiol (with no break in treatment) versus placebo in women with an intact uterus	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (68) [10]	Premenstrual symptoms	Continuous subcutaneous estradiol implant (with no break in treatment) versus placebo in women with an intact uterus	4	–1	0	–2	0	Very low	Quality point deducted for sparse data; directness points deducted for high attrition

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

© BMJ Publishing Group Ltd 2015. All rights reserved.