Overweight, Obesity and Contraception: FSRH CEU Response to Public Consultation

The FSRH CEU would like to thank the individuals and representatives from our stakeholder organisations who have provided feedback.

<table>
<thead>
<tr>
<th>Individual /organisation</th>
<th>Location in guideline</th>
<th>Comments</th>
<th>CEU’s Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual/FSRH and CEC Member</td>
<td>Page 12, Line 4, second DMPA recommendation</td>
<td>This could unfortunately be interpreted by clinicians and women as saying that all or most women may gain weight. This could put clinical practice back a few years as we have tried to counter this potential myth. It would be more helpful to repeat the recommendation wording from the POI guidance (2014) which includes the additional information “… particularly in women under 18 with a BMI of &gt; 30” and the second one that states: “Women who gain more than 5% of their baseline body weight in the first 6 months of DMPA use are likely to experience continued weight gain.”</td>
<td>Thank you for this feedback. The Guideline Development Group (GDG) have reconsidered this changed the Key Information to read: “DMPA use appears to be associated with some weight gain, particularly in women under 18 years of age with a body mass index (BMI) ≥30 kg/m².”</td>
</tr>
<tr>
<td>Individual/FSRH Member</td>
<td>General comments</td>
<td>Study details could possibly be put in smaller/different font or separate box to make it easier to skip past them for those to whom they are not relevant. This may, of course, already be addressed in your final edit format.</td>
<td>Thank you for this feedback. We agree we have shortened the document or made the presentation of information more concise where possible, but have included the study details in text per our standard guideline formatting.</td>
</tr>
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</table>
The phrasing of this paragraph comes across as quite stigmatising, implying that women with obesity should be prevented from embarking on pregnancy and that they are going to harm the next generation too! Please rephrase to bring a positive emphasis to supporting women with obesity to plan pregnancy, the benefits of ‘getting fit for pregnancy’, to seek additional support to reduce known risks associated with obesity in pregnancy and to convey the risks and impact in a motivational rather than crushing way.

Thank you for this feedback. We have revised the wording of this paragraph but have retained the factual information on the increased maternal risk and inter-generational health effects of maternal obesity.

This should include all staff having access to scales that weigh up to 200kg. I am not sure where this recommendation would best fit in the guideline.

Thank you for this feedback. We have added the following Practical Consideration to Section 7: “Facilities providing contraceptive care should have weighing scales that can accurately measure high body weights.”

BMI 30-34 is sadly not uncommon. The guidance states that these women cannot use the DMPA if they smoke (even if they are trivial smoker), yet the evidence is not there to back this statement up. This limits a woman’s options at a mildly obese level.

Thank you for making this point. No revisions have been made based on this.

Some guidance as to what levels of diarrhoea would prove problematic for those using CHC

Thank you. There is no evidence on which to base guidance as to what levels of diarrhoea would be potentially problematic in this situation so we have decided against including specific guidance to this effect. No revisions have been made based on this.
Potential barrier to uptake Women using SC DMPA have an increased risk of lipoatrophy—might be useful to mention this in the guideline

General comments Would have welcomed a comment on use of COC in PCOS. These women may be obese but use the COC for health and not just contraceptive reasons

FPA General comments It may be beneficial to include a point on the other forms of contraception within the executive summary (i.e. barrier, permanent and fertility awareness methods).

Page 9, line 9 PK as an abbreviation of pharmacokinetic is not outlined.

vi. Reference to UKMEC 1/2/3 is made before the table. This means the implications of the grading system are not immediately clear. It may be beneficial to include a key which explains the numerical evidence levels (e.g. evidence level 2+).

Thank you for this important comment. We have done a literature search on this topic and found that there is no evidence to show this is a more significant problem for women of certain weight groups, and there is no reason to believe it would affect women with obesity more than women without. Thus, we have chosen not to mention the issue of lipoatrophy in this guideline. No revisions have been made based on this.

We have included a mention of “management of symptoms associated with polycystic ovarian syndrome” in Section 5.5.4 Health benefits of CHC.

Thank you. The Executive Summary of Recommendations only includes the Key Information and Clinical Recommendations that have been made by the GDG and are included in the body of the document. As no Key Information or Clinical Recommendations have been developed by the GDG for barrier, fertility awareness and permanent methods, we cannot include them in the Executive Summary of Recommendations. No revisions have been made based on this.

Thank you. We have amended the document accordingly.

Thank you for this feedback. We have now included a link to Table 1 which explains the UKMEC categories the first time that reference to the UKMEC appears in the document. The grading information is included in Appendix 1.
Currently states ‘Double dose POP is not recommended for women who are overweight or women with obesity.’ I agree that it is unnecessary routinely to use double for high BMI however we do sometimes use double Desogestrel off license to manage irregular bleeding for individual patients and the current wording could make this problematic. Could this be reworded e.g. not routinely recommended or we recommend standard dose pop are used for women with high BMI.

Thank you. We have revised the Clinical Recommendation as follows: “Double dose POP for contraception is not recommended for women who are overweight or women with obesity.”

Very useful to have a column for UKMEC if obesity is one of multiple risk factors to highlight this element

Post bariatric surgery is UKMEC 2 for BMI 30-34 for CHC, and POP UKMEC 1 for all BMI post bariatric surgery when previous advises avoidance of OC post bariatric surgery – I understand this is for safety only vs efficacy but could cause confusion – could it be marked as not recommended or see text?? Could this sentence from page 5 be added in after the table in the summary to highlight this– ‘It is important to note that UKMEC categories for contraceptive use after bariatric surgery relate to safety of use rather than effectiveness. Safety considerations after bariatric surgery relate to ongoing high BMI. In Section 6.2 (Weight loss surgery and contraception) of this guidance, the CEU advises the following: Women should be advised that the effectiveness of oral contraception (OC), including oral emergency contraception, could be reduced by bariatric surgery and OC should be avoided in favour of non-oral methods of contraception.”

Evidence very wordy and could be more concisely conveyed – ‘Two retrospective cohort studies reporting on very small numbers of patients with portomesenteric vein thrombosis (n=17 and n=5) after
laparoscopic sleeve gastrectomy [247,248], reported OC use (unspecified type) in some patients with this complication (n=7 and n=1, respectively), but also no contraceptive use or contraceptive implant use in others. No comparative information is included on OC use among women who did not develop portomesenteric vein thrombosis post-bariatric surgery, so no conclusions about any relationship between OC use and portomesenteric vein thrombosis can be drawn. A 2018 systematic review and meta-analysis [249] on portomesenteric vein thrombosis after a bariatric procedure included 41 studies with a total of 110 patients. The authors reported that 35.4% of the patients were on OCs (type unspecified), however no information was collected on OC type, when the OC used or whether it was stopped for surgery/post-operative period. None of these studies were designed to look at contraceptive safety, all had very small numbers and no meaningful contraceptive comparison groups, and were conducted in a population at high risk for thrombotic events irrespective of contraceptive use so these data are generally uninformative.’ Text not in bold could be removed

**Individual/FSRH Member**

**General comments**

Very helpful

Thank you for this feedback on Section 7.

Would be good to have a clearer flow chart for use of how to advise on oral EC

Thank you for this feedback. We will consider whether this would be possible and useful as we develop the Primary Care Quick Reference Summary for this guideline. Related
That seems too vague for a guideline. Surely there is some evidence to demonstrate that DMPA is associated with weight gain is the comment to write. Remove the word some not helpful for GPs when discussing this method. It either does in some women or it does not cause weight gain.

That comment is not necessary here.

Thank you for this feedback. The GDG have reconsidered this and revised the Key Information to read: “DMPA use appears to be associated with some weight gain, particularly in women under 18 years of age with a body mass index (BMI) ≥30 kg/m^2.”

Thank you. We have tried to ensure that this wording aligns closely with UKMEC 2016 and UK FSRH Guideline *Combined Hormonal Contraception*.

Thank you for this feedback. The current recommendations and content are worded to align with the existing UK FSRH Guideline *Emergency Contraception*.

Thank you. Final placement of the tables and figures will be done in copy editing and typesetting and we may or may not be able to place this table as you suggest.
contraceptive methods on weight"

Page 9
Be clear that PK= pharmacokinetics

Thank you. This has been clarified.

Page 10, paragraph 5
This comment is really important and one that GPs often ask during teaching sessions. I am not sure that most GPs will find it written here at the end of a complex data section. Can this be highlighted better?

Thank you. We agree that this is important and as such have made it a Clinical Recommendation. We will ensure this point is highlighted in the Primary Care Quick Reference Summary for this guideline.

Page 13, paragraph 2
Should there be a comment about DMPA-IM and DMPA-SC being similar effects. Again a comment that is often asked by GPs?

Thank you. We will ensure this point is highlighted in the Primary Care Quick Reference Summary for this guideline.

Page 14, paragraph 2
This is such an important practical point for primary care. Comment on this in the practical issues section - advice about doing BMLs on women when they receive their DMPA and offer advice about alternative method use in women who gain weight in the first 6 months as it is likely that weight gain will continue.

Thank you. We will consider addressing this in the Primary Care Quick Reference Summary for this guideline.

section 5.3.5 I please add something about weight monitoring in this section - see comment above

Thank you. As above, we will consider addressing this in the Primary Care Quick Reference Summary for this guideline.

section 5.3.5 Remove (upper arm)"- this is a guideline

Thank you for your feedback. The GDG felt this wording should remain.

section 5.3.5 Remove ‘green’ and ‘blue’ from the needle descriptions

Thank you for your feedback. The GDG felt this wording should remain.
<table>
<thead>
<tr>
<th>Section/Paragraph</th>
<th>Original Text</th>
<th>Revised Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>section 5.5.4</td>
<td>Androgenic symptoms - doesn't help with psychological symptoms</td>
<td>Thank you for your feedback. The GDG wished to include this more general statement.</td>
</tr>
<tr>
<td>Page 24, last paragraph</td>
<td>This is such an important point for primary care is it possible to highlight it better</td>
<td>Thank you. We will ensure this point is highlighted in the Primary Care Quick Reference Summary for this guideline.</td>
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<tr>
<td>Table 3</td>
<td>This is confusing putting this here. This is about contraceptive safety so should be placed above the section on contraceptive efficacy to avoid confusion</td>
<td>Thank you for your feedback. The final location of this table will depend on the typesetting of the document.</td>
</tr>
<tr>
<td>Page 31, para 2</td>
<td>should there be a comment about DMPA and weight gain here. Not something women who have had bariatric surgery will want</td>
<td>Thank you. We will ensure this is addressed this issue in the Primary Care Quick Reference Summary for this guideline.</td>
</tr>
<tr>
<td>Page 31, para 5</td>
<td>Re: &quot;POC&quot;: haven't seen this abbreviation used previously in this guideline - need to check and then clarify if not</td>
<td>Thank you. We have rectified this.</td>
</tr>
<tr>
<td>Page 31, &quot;Many HCPs feel concerned they may cause offense when discussing weight&quot;</td>
<td>Remove this comment. It is important that we discuss weight</td>
<td>Thank you. The FSRH CEU and the GDG agree that this is an important topic to discuss, and that is why it has been explicitly mentioned in the guideline. The GDG discussed this statement in depth and decided it should be included in the guideline based on the feedback from patient representatives and peer reviewers.</td>
</tr>
<tr>
<td>Page 32, &quot;The GDG suggests that safe principles include&quot;</td>
<td>Not sure that this is relevant</td>
<td>Thank you. Including this information was suggested by patient representatives and peer reviewers.</td>
</tr>
<tr>
<td>General comments</td>
<td>Recommendation to do BMI on all women attending for contraception and then repeat either next contraception visit (depo) or if the woman returns complaining of weight gain so that this can be checked to see if the gain is perceived or real. There is a possibility of doing a study on this using the RCGP data base if you wanted to.</td>
<td>Thank you. We will consider addressing this in the Primary Care Quick Reference Summary for this guideline.</td>
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Barriers:
Much of the recommendation is not supported by good evidence.

"Chapter 5.8.2. However, use of 3 mg LNG-EC (which is well tolerated and is supported by pharmacokinetic data) is justified by its potential ability to prevent unintended pregnancy more effectively than the standard 1.5 mg dose in women weighing >70 kg or with a BMI >26 kg/m2.

Here it must be pointed out that the study which is the basis of this recommendation did not examine the overweight BMI category. The scope of the study was to recruit only normal and obese women therefore there is no evidence for that in 26-30 kg/m² BMI range doubling the dose of LNG-EC would be more effective than the standard 1.5 mg.

In addition, these results should be interpreted with caution as the sampling period is quite short (truncated at 2.5 hrs) and the sample size is too small (1). LNG has a relatively long half-life of 26 hours with a Tmax of about 2 hours. Guidelines for regulatory submissions (Guideline on the investigation of bioequivalence: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) require that the sampling schedule should include frequent sampling around predicted Tmax to provide a reliable estimate of peak exposure. It should also cover the plasma concentration time curve long enough to

Thank you for this feedback. The CEU has considered this issue before and this information and these recommendations are part of existing UK FSRH CEU guidance. This issue was reconsidered in the development of this guideline and the UK FSRH CEU Guidance Development Group has decided to continue with this guidance as it currently is.
provide a reliable estimate of the extent of exposure. Whilst it is acknowledged that this study was not conducted for a regulatory submission, the limited number of data points around Tmax is a limitation of this study. Therefore, the AUC is not adequately characterised and the possibility that the Tmax and Cmax were missed in some subjects cannot be excluded. Furthermore, in August 2017 CMDh requested the Marketing Authorisation Holders (MAHs) of levonorgestrel containing contraceptives Levonelle: MAH, Gedeon Richter Plc and Norlevo: MAH, HRA Pharma to submit a variation work-sharing procedure for Levonorgestrel containing products indicated in emergency contraception to assess the implications of these data. The UK for Levonelle was assessing the variation submitted by Gedeon Richter Plc and a parallel variation for Norlevo was ongoing and was being assessed by Germany. Norlevo is not approved in the UK. This work-sharing variation evaluated the implications of the all new data available since the finalisation of the Article 31 referral procedure (EMEA/H/A-31/1391; 2014) on emergency contraceptives containing LNG or ulipristal acetate (UPA). Two of the recently available articles, Edelman et al, 2016 (1) and Praditpan et al, 2017(2) evaluated the effect of BMI on the pharmacokinetics (PK) of levonorgestrel emergency contraceptives. The results of the
studies suggest alteration in PK parameters of levonorgestrel with BMI >30 kg/m². “During the evaluation it was agreed that the results of the two PK studies suggest that BMI has a strong impact on serum concentrations of levonorgestrel, it is considered however that the clinical relevance of the data is questionable for the following reasons:

• The biologically active free LNG concentration was reduced to a smaller extent;
• The fraction of unbound LNG was approximately 35% higher in obese women when compared to non-obese women, due to the lower SHBG levels observed in obese women;
• The studies were not designed to measure and did not measure endpoints directly related to effectiveness.”

According to the outcome of the work-sharing procedure the benefit-risk balance of LNG-EC remained positive for women of all body weight and BMI. It should be taken as soon as possible following unprotected intercourse or contraceptive failure regardless of body weight/BMI in order to maximise the likelihood of preventing unintended pregnancy. Furthermore, the available data are considered insufficient to support the inclusion of definite BMI or body weight parameters in the product information as no clear-cut points can be defined at present.
After a thorough evaluation the UK MHRA required changes in the SmPC with the following wording:

3.S 5.2 The paragraph should be amended with a separate heading: “Pharmacokinetics in obese women.” A pharmacokinetic study showed that levonorgestrel concentrations are significantly decreased in obese women (BMI $\geq$ 30 kg/m²) (approximately 50% decrease in Cmax and AUC0-24), compared to women with normal BMI (< 25 kg/m²) (Praditpan et al., 2017). Another study also reported a decrease of levonorgestrel Cmax by approximately 50% between obese and normal BMI women, while doubling the dose (3 mg) in obese women appeared to provide plasma concentration levels similar to those observed in normal women who received 1.5 mg of levonorgestrel (Edelman et al., 2016). The clinical relevance of these data is unclear.” Additionally, having new publication regarding this topic (3), the available data are considered insufficient to support the aforementioned dose adjustment in overweight or obese women. This article reviews the evidence relating to the effect of obesity on the pharmacokinetics and clinical efficacy of LNG-EC and confirms that currently available data are inadequate to draw definite conclusion regarding the impact of BMI on the efficacy of LNG-EC. Although PK studies indicate that obesity is associated
with reduced exposure to LNG-EC, there is
no substantive evidence that this affects its
PD properties or clinical efficacy.
On behalf of Gedeon Richter Plc. I would like
to express our concern regarding the strength
of the evidence supporting doubling the dose
above BMI 26 kg/m² or 70 kg bodyweight.

References
(1) Edelman Alison B, Cheralal Ganesh, Blue
Steven W, Erikson David W, Jensen Jeffrey
T. Impact of obesity on the pharmacokinetics
of levonorgestrel-based emergency
contraception: single and double dosing,
Contraception (2016)
(2) Praditpan P, Hamouie A, Basaraba CN,
Nandakumar R, Cremers S, Davis AR. et al.
Pharmacokinetics of levonorgestrel and
ulipristal acetate emergency contraception in
women with normal and obese body mass
(3) Kardos L, Magyar G, Schvab E, Luczai E.
Levonorgestrel emergency contraception and
bodyweight. Current Medical Research and
Opinion (2018)
Other comments

Overall usefulness

CEU response to comments below:

Thank you. We are grateful for the very kind comments from reviewers about the value and usefulness of this guideline to improving clinical practice and ensuring that the highest quality of contraceptive care is provided to women who are overweight and women with obesity in the UK.

Individual/FSRH member

Very useful, practical, easy to follow, logical order, well laid-out. Very welcome addition to the FSRH CEU library of resources

Individual/FSRH member

Useful relevant practical. Excellent important document bringing together all relevant elements. Length will put off non specialists but summary useful.

Individual/FSRH member

Useful-obesity is a common problem. Tables are good. Good initial summary. Good to know there is no need to replace the implant early in obese women. Great tips on how not to give offence when discussing weight.

Individual/FSRH member

Very useful.

Individual/FSRH member

Brilliant guideline. Very useful for primary care. Easy to read the relevant parts. Some of the most relevant points for primary care are hidden in the detail and this is not where GPs will look. There is a need for the relevant facts that patients will ask to be highlighted for easy access. It is good to have something to back up the discussions we have with women about weight gain – myth buster. Good to have guidance on an increasingly important issue.

FPA

The opening recommendations (including the clinical recommendations) outlined in the executive summary, Resource 1 and the practical considerations within the main body of the text are particularly helpful. The section on weight loss medication and contraception is very welcome and useful. The section on weight loss surgery and contraception is also very welcome including the recommendations for future research as, it appears, there is a paucity of evidence in this area which leaves questions and recommendations unanswered. The future FSRH document on the effects of the contraceptive methods on weight would be a very useful edition to this document. Clear recommendations will help facilitate implementation.

Guideline layout, writing style and length

CEU response to comments below:

Thank you for this feedback. We fully acknowledge that the guideline is lengthy. The guideline was written with a digital format in mind. We anticipate users will go directly to specific sections and therefore feel that it is important for each section have enough information to be a stand-alone document. Where possible, to avoid duplication of text, readers have been signposted to the relevant sections of the guideline for further details.

Individual/FSRH member

Writing style Easy to read, good use of normal English. Structure/layout: Very good. Length seems appropriate.
All comments on the FSRH Overweight, Obesity and Contraception can be sent directly to the CEU via the FSRH website (www.fsrh.org).

The Clinical Effectiveness Unit (CEU) was formed to support the Clinical Effectiveness Committee of the Faculty of Sexual and Reproductive Healthcare (FSRH), the largest UK professional membership organisation working at the heart of sexual and reproductive healthcare. The CEU promotes evidence based clinical practice and it is fully funded by the FSRH through membership fees. It is based in Edinburgh and it provides a member’s enquiry service, evidence based guidance, new SRH product reviews and clinical audit/research. Find out more here.