The College of Sexual & Reproductive Healthcare

SUPPLEMENTARY EVIDENCE TABLES

Additional information to support the

UK MEDICAL ELIGIBILITY CRITERIA

FOR CONTRACEPTIVE USE | UKMEC 2025

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INTRODUCTION

The UK Medical Eligibility Criteria for Contraceptive Use (UKMEC)

This document provides supplementary information to accompany and support the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) 2025. It provides a summary of the evidence that was presented to the Guideline Development Group (GDG), and which underpinned the decision-making process. The tables below cover each of the topics that were reviewed as part of the 2025 update. Further information about the UKMEC including the development process can be found within the main UKMEC guidance.

Contents

1. Topic: Postpartum contraception 1
2. Topic: Smoking (e-cigarettes) 6
3. Topic: Hypertension 8
3.1 Hypertension – definition 8
3.2 Hypertension and hormonal contraception 9
3.3 Adequately controlled hypertension [supplementary evidence] 10
4. Topic: Stroke 12
5. Topic: Risk of venous thromboembolism (VTE) 16
5.1 Use of progestogen-only contraception in individuals at increased risk of VTE 16
5.2 Personal characteristics and conditions linked to increased risk of VTE [supplementary evidence] 20
5.3 Cancer type and risk of VTE [supplementary evidence search] 21
6 Topic: High risk Human Papillomavirus (HPV) 23
7 Topic: Breast conditions – BRCA carriers 26
8 Topic: Ovarian cancer 28
9 Topic: Sexually transmitted infections (STIs) 31
9.1 Herpes Simplex Virus (HSV) 31
9.2 Chlamydia (CT) 31
9.3 Gonorrhoea (GC) 32
9.4 Syphilis (STS) 34
9.5 Trichomonas Vaginalis (TV) 34
9.6 Mycoplasma Genitalium (MG) 35
10 Topic: High risk of Human Immunodeficiency Virus (HIV) 37

11 Topic: Liver disease 40
12 Topic: Sickle cell disease and trait 43
12.1 Sickle cell disease 43
12.2 Sickle cell trait 47
13 Topic: Chronic Kidney Disease 49
14 Topic: Osteoporosis and osteopenia 54
15 Topic: Multiple sclerosis 57
16 Topic: Progestogen-only pill – Drospirenone 62
17 Topic: Combined Hormonal Contraception – Estetrol with Drospirenone 65

1. Topic: Postpartum contraception

PICO							
Population	Individuals of reproductive age during postpartum period						
Intervention	Intrauterine contraception inserted at different time points as per UKMEC (specific focus on from 48h to less than four weeks)						
Comparator	Any other timing or no comparator						
Outcomes	Expulsion, perforation, infection, malposition, breastfeeding outcomes						
Study design	Observational and interventional studies						
Preface	A systematic search of medical literature (a single database, from 2015 to January 2025) returned a large quantity of studies (68 original studies and 11 systematic reviews); however, many of them are limited by: sample size, short follow-up period/follow-up poorly described/follow-up limited (e.g. self-reported not clinical examination), significant numbers lost to follow up, and poorly defined timeframes (studies use similar descriptions to describe different timeframes). Earlier studies have suggested that post-placental insertion of an intrauterine device (IUD) may be associated with lower expulsion rates than later insertions. Consequently, most recent studies have focused on post-placental insertion ("immediate insertion"). To provide the most relevant evidence reflective of the clinical practice in the UK, we have focused the inclusion criteria to: • **Intervention**: IUD insertion between 48 hours and less than four weeks. • **Comparator**: IUD insertion at any other time point. Four publications met the modified criteria (1–4) – a systematic review (1), a randomised trial (4), and two reports from the APEX-IUD cohort study (2,3).						
Outcome	**No. of studies, study design (number of participants)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Effect measure**	**Certainty of evidence**
Comparison: >10 min to < three days postpartum (inpatient) [no comparator]							
IUD expulsion	11 observational studies (2,044 participants)(1,5)	Serious[a]	Nonserious	Nonserious	Serious[b]	Rate 25.1% (range 3.5–46.7)	Very Low

Outcome	No. of studies, study design (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Certainty of evidence
Comparison: 0 to < three days postpartum (inpatient) vs non postpartum							
Uterine perforation	1 observational study (231,622 participants) (3)	Nonserious	Not applicable	Nonserious	Nonserious	aHR 2.73 (95%CI 1.33, 5.63)*	Low
IUD expulsion	1 observational study (231,622 participants) (2)	Nonserious	Not applicable	Nonserious	Nonserious	aHR 5.34 (95%CI 4.47, 6.39)	Low
Comparison: Within 3 days postpartum (inpatient) [no comparator]							
IUD expulsion	12 observational studies (8,702 participants) (1,5)	Serious[a]	Nonserious	Nonserious	Serious[b]	Rate 7.1% (range 1.4–29.8)	Very Low
Comparison: Three days to < four weeks postpartum (outpatient) [no comparator]							
IUD expulsion	4 observational studies (17,408 participants)(1,5)	Serious[a]	Nonserious	Nonserious	Nonserious	Rate 2.0% (range 0.0–2.1)	Very Low
Comparison: Three days to < four weeks postpartum (outpatient) vs ≥ four weeks postpartum							
IUD expulsion	NR (1)	Serious[a]	Not applicable	Nonserious	Very serious[c]	aRR 9.51 (95%CI 0.63, 19.52)	Very Low
Comparison: Four days to ≤ six weeks postpartum (outpatient) vs non postpartum insertion							
Uterine perforation	1 observational study (246,106 participants)(3)	Nonserious	Not applicable	Nonserious	Nonserious	aHR 6.71 (95%CI 4.80, 9.38)*	Low
IUD expulsion	1 observational study (246,106 participants) (2)	Nonserious	Not applicable	Nonserious	Nonserious	aHR 1.22 (95%CI 1.05, 1.41)	Low
Comparison: Three weeks vs ≥ four weeks postpartum							
IUD expulsion	12 observational studies (8,702 participants) (1,5)	Serious[a]	Nonserious	Nonserious	Serious[b]	Rate 7.1% (range1.4–29.8)	Very Low

Outcome	No. of studies, study design (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Certainty of evidence
Comparison: Two to four weeks vs ≥ six weeks postpartum							
IUD expulsion (any)	1 randomised trial (294 participants) (4)	Serious[d]	Not applicable	Nonserious	Very serious[c]	RD 3.8 (95%CI -3.1, 10.9)	Very Low
IUD malposition	1 randomised trial (294 participants) (4)	Serious[d]	Not applicable	Nonserious	Serious[e]	RD 5.4 (95%CI 2.1, 10.2)	Low
Pelvic infection	1 randomised trial (294 participants) (4)	Serious[d]	Not applicable	Nonserious	Serious[f]	RD 2.0 (95%CI -0.5, 5.7)	Low
Uterine perforation	1 randomised trial (294 participants) (4)	Serious[d]	Not applicable	Nonserious	Very serious[g]	None	Very Low

Abbreviations: a, adjusted; CI, confidence interval; IUD, intrauterine device; RD, risk difference; RR, risk ratio.

*Rate of perforation per 1000 person-years: 0 to 3 days 2.37 (95%CI 1.18, 4.24), 4 days to ≤ six weeks 5.53 (95%CI 4.75, 6.4), non-postpartum 0.68 (95%CI 0.61, 0.76).

Footnotes

a. Downgraded by one level for risk of bias (concerns over selection bias, follow-up rates & duration of follow-up, variable definitions & detection of expulsion)(5)
b. Downgraded by one level for imprecision (due to wide range of expulsion rates across the studies)
c. Downgraded by two levels for imprecision (wide confidence interval crossing line of no difference)
d. Downgraded by one level for risk of bias (concerns over loss to follow-up/dropout rate >20%)
e. Downgraded by one level for imprecision (wide confidence interval)
f. Downgraded by one level for imprecision (due to confidence interval crossing line of no difference).
g. Downgraded by two levels for imprecision (due to study not being powered to detect this outcome; no events)

Additional considerations

Evidence from randomised trials on immediate vs delayed insertion

A Cochrane review of randomised trials compare the initiation, utilisation (at 6 and 12 months after delivery), effectiveness, and adverse effects of immediate versus delayed postpartum insertion of implants and IUDs for contraception. (6) The review authors defined immediate insertion as 0 min to hospital discharge

and delayed insertion as more than four weeks. The review included 11 RCTs of IUDs (1 894 participants) and evaluated effect on following outcomes: IUS insertion rates, IUS expulsion rate (6, 12 and 24 months after delivery), utilisation rate (6, 12, and 24 months after delivery), adverse events (perforation and infection), satisfaction, unintended pregnancy, breastfeeding at six months.

Compared to delayed insertion (≥ four weeks), immediate insertion may lead to higher expulsion rates at 6 months after delivery (RR 4.55, 95%CI 2.52, 8.19; 8 studies, 1 206 participants; I^2 = 31%; *low-certainty evidence*) and it was uncertain whether immediate insertion leads to a difference in breastfeeding rates at 6 months after delivery (RR 0.90, 95%CI 0.63, 1.30; 5 studies, 435 participants; I^2 = 54%; *very low-certainty evidence*). No included study reported on adverse effects of IUDs.

Evidence on safety of immediate insertion

A systematic review of interventional and observational studies evaluated IUD utilisation and safety within 12 months of immediate postpartum insertion (from delivery up to 36 h), and its efficacy within 18 months. (7) The review included 61 interventional and 72 observational studies, the findings were stratified by country income status (higher- vs lower-income).

Overall, insertion of IUDs postpartum was associated with low rate of complications such as abnormal bleeding, uterine infections, or perforations. In high income setting the proportion of individuals with infections after immediate IUD insertion ranged from 0-3% in 14 out of 14 studies reporting the events. Occurrence of two perforations was reported across 12 studies.

The US Medical Eligibility Criteria for Contraception Use 2024 update

The US MEC 2024 update (5) introduced following changes to safety of IUS insertion postpartum.

- Immediate insertion (defined as < 10 minutes) - change from category 1 to category 2.

The rationale for the change was based on the following: postpartum placement of IUDs is safe and does not appear to increase health risks associated with IUD use such as infection. Higher rates of expulsion during the postpartum period should be considered as they relate to effectiveness, along with patient access to interval placement (i.e., not related to pregnancy) when expulsion rates are lower.

There has been no change to timings and no change to the category 10 minutes to < 4 weeks, which is a USMEC 2 for IUC insertion.

Abbreviations: a, adjusted; CI, confidence interval; HR, hazard ratio; MEC, Medical Eligibility Criteria; RCT, randomised controlled trial; RR, risk ratio; IUD, intrauterine device; US, the United States of America.

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2. Topic: Smoking (e-cigarettes)

PICO	
Population	Women of reproductive age using e-cigarettes/vaping
Intervention	Any hormonal contraceptive method or copper intrauterine device
Comparator	Alternative contraceptive method or no contraceptive method
Outcomes	Cardiovascular risk
Preface	A systematic search of medical literature (two databases, from inception to October 2024) identified one case study (1) describing a single case of a 22-year-old who developed bilateral pulmonary emboli and subacute CVA whilst vaping and using CHC. No other direct evidence was found for the use of both e-cigarettes and any contraceptive method. Three umbrella reviews (2-4) and three systematic reviews (5-8) of indirect evidence were found, assessing the risk of cardiovascular disease with e-cigarette use. These are summarised below.

Additional considerations

Fadeyi (2023) - case study describing a case of a 22-year-old who developed bilateral pulmonary emboli and subacute CVA whilst vaping and using CHC. (1)

Riley (2016) - a systematic review of articles reporting myocardial infarction (MI), stroke, venous thromboembolism, peripheral arterial disease or changes to CV markers in women using e-cigarettes and hormonal contraception (HC). They found no articles that reported on outcomes among e-cigarette users using HC. (8)

Martinez-Morata (2020) - a systematic review of studies evaluating the relationship between e-cigarettes and blood pressure. Fourteen studies were identified. All trials included at least one e-cigarette arm with nicotine, 6 a no-nicotine e-cigarette arm, and 3 a placebo arm. Intervention studies on the short-term effects of e-cigarette use on blood pressure endpoints showed a consistent increase of blood pressure immediately to several hours after exposure to e-cigarettes containing nicotine, variable changes after exposure to non-nicotine e-cigarettes, including significant increases of SBP and/or DBP, and no changes when using a placebo device. This SR supports the hypothesis that use of e-cigarettes both with and without nicotine result in short term elevation of both systolic and diastolic blood pressure. (5)

Sharma (2023) - a systematic review and meta-analysis of 4 papers (585,306 subjects), looking at myocardial infarction in e-cigarette users. The odds of suffering from MI were 33% higher in e-cigarette users than people who had never used e-cigarettes. The OR of having an MI in e-cigarette (e-cigarettes only or e-cigarettes + traditional smoking) users was 1.33 (95%CI = 1.14, 1.56, p = 0.01) in comparison to non-e-cigarette users (traditional smoking or no smoking). While the OR was 0.61 (95%CI = 0.40, 0.93, p = 0.02) when compared with traditional smoking. (6)

Siddiqui (2023) - a systematic review and meta-analysis of 27 studies (n = 863) looking at acute cardiovascular effects of e-cigarettes. Results demonstrate that using nicotine e-cigarettes is associated with a significant increase in short-term cardiovascular hemodynamic measures and biomarkers, including heart

rate, SBP, DBP, MAP, AIx75 and decrease in flow mediated dilatation (FMD). However, the clinical significance, in terms of health deterioration, of these effects was not studied. (7)

Banks (2023) - an umbrella and systematic review of 400 studies. Found that evidence regarding the health outcomes of e-cigarettes was lacking. There was moderate evidence that nicotine e-cigarettes immediately increase heart rate, systolic and diastolic blood pressure, and arterial stiffness acutely after use, by smokers. Evidence is insufficient or unavailable regarding the effects of nicotine and non-nicotine e-cigarette use on cardiovascular disease. (2)

Asfar (2022) - an umbrella review conducted to inform health communication strategies regarding electronic nicotine delivery systems (ENDS). Ninety systematic reviews were evaluated overall, of which 6 reported on CVD outcome. Three of these reviews indicated a possible association between ENDS and CVD. One review demonstrated that ENDS use (with/without nicotine) might result in short-term elevations of both systolic and diastolic blood pressure (BP). In another review, most included studies (75%) found potentially harmful effects of ENDS on CVD through inducing sympathetic nerve activation, oxidative stress, endothelial dysfunction and platelet activation. Both in vitro and in vivo studies showed increased reactive oxygen species production and a reduction in antioxidants after ENDS exposure, constituting an atherosclerotic risk. Overall, this umbrella review found limited but suggestive evidence ENDS use increases risk of CVD. (3)

Peruzzi (2022) - an umbrella review of 7 systematic reviews, which included those in Asfar (2022), but also a screening of case reports looking at adverse events associated with e-cigarette use, which found two case reports of cardiovascular disease associated with e-cigarette use (a case of acute myocardial infarction in a young man and a case of atrial fibrillation in an elderly woman). The umbrella review concluded that although there is limited data, e-cigarette use is associated with increased cardiovascular risk but may be less than tobacco smoking. (4)

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3. Topic: Hypertension

3.1 Hypertension – definition

Aim	To investigate whether the blood pressure parameters currently mentioned in the UK MEC (values representing “normal” or “elevated”) align with those used in the clinical practice and current hypertension guidelines in the UK.
Existing UKMEC blood pressure classification (1)	**NICE classification (2)**
Adequately controlled hypertension	Below 140/90 in those under 80 years of age
Consistently elevated blood pressure levels (properly taken measurements)	See below
(i) SBP >140-159 mmHg or DBP >90-99 mmHg	**Stage 1** hypertension— clinic blood pressure 140/90 mmHg to 159/99 mmHg and subsequent ambulatory blood pressure monitoring (PM daytime average) or home blood pressure monitoring average BP 135/85 mmHg to 149/94 mmHg.
(i) SBP ≥ 160 mmHg or DBP ≥ 100 mmHg	**Stage 2** hypertension — clinic blood pressure 160/100 mmHg or higher but less than 180/120 mmHg and subsequent ambulatory blood pressure monitoring daytime average or home blood pressure monitoring average blood pressure 150/95 mmHg or higher. **Stage 3** or severe hypertension — clinic SBP 180 mmHg or higher or clinic DBP 120 mmHg or higher.
Commentary	
The above classifications were discussed with the subject expert and addressed during the guideline development group meeting.	

3.2 Hypertension and hormonal contraception

PICO	
Population	Individuals of reproductive age with hypertension
Intervention	Hormonal contraceptive methods
Comparator	Alternative hormonal contraceptive method or no hormonal contraception
Outcomes	Adverse health outcomes especially cardiovascular
Study design	Observational and interventional studies
Preface	A systematic search of medical literature (two databases, from 2005 to February 2025) returned no relevant studies. Relevant indirect evidence on the effect of contraceptive methods on blood pressure levels and hypertension in the general population was identified in the literature search. The summary of their findings is presented below.

Additional considerations

A systematic review of observational studies from 2022 (3) evaluated the effect of non-oral hormonal contraceptives on the risk of hypertension and changes in blood pressure measures compared to non-HC and OC options. Only one included study reported on the incidence of hypertension (the criteria for hypertension were not defined). The study was conducted in Thailand (4) and compared long-term (>120 months) use of DMPA (50 individuals) with Cu-IUD (50 individuals) in normotensive individuals. Hypertension was recorded in 10% (5/50) DMPA and 14% (7/43) of Cu-IUD users.

Compared to non-HC users, use of DMPA was associated with increased blood pressure (SBP: 3.24 mmHg, 95%CI 2.49 to 3.98 mmHg; DBP: 3.15 mmHg, 95%CI 0.09 to 6.20 mmHg), the use of hormonal IUS was associated with reduced blood pressure (SBP: -4.50 mmHg, 95%CI -8.44, -0.57 mmHg; DBP: -7.48 mmHg, 95%CI -14.90, -0.05 mmHg), and use of the vaginal ring was associated with reduced only in DBP (-3.90 mmHg, 95%CI -6.67, -1.13 mmHg). Compared to OC use, DMPA was associated with increased diastolic BP (2.38 mmHg, 95%CI 0.39, 4.38 mmHg).

A systematic review of randomised trials from 2024 (5) examining an association between the use of OC (mostly COC) and the occurrence of systemic hypertension found minor variations in blood pressure values with the use of OC. The authors concluded that observed differences were not meaningful enough to merit any specific clinical recommendations.

Interpretation of blood pressure changes

When interpreting the changes in blood pressure, it's important to consider the perspective as a 2 mm change for an individual may not carry any or very little increase in cardiovascular risk. At the same time, on a populational level, this may translate into a meaningful number of strokes. The age of a target population is an important factor to consider when evaluating cardiovascular risk.

Abbreviations: COC, combined oral contraceptive; Cu-IUD, copper intrauterine device DBP, diastolic blood pressure; DMPA, depot medroxyprogesterone acetate; HC, hormonal contraception; IUS, intrauterine system; NICE, The National Institute for Health and Care Excellence; OC, oral contraceptives; SBP, systolic blood pressure; UK, The United Kingdom.

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3.3 Adequately controlled hypertension [supplementary evidence]

Aim	Is there sufficient evidence to change the MEC category 3 for adequately controlled hypertension?

Summary of evidence

- COC promotes greater activation of the RAAS with estrogen component probably primarily being responsible for blood pressure changes. (1)
- Estetrol, a natural estrogen, probably having less effects on the RAAS compared with ethinyl estradiol. (2)
- A systematic review of observational studies from 2022 (3) evaluated the effect of non-oral hormonal contraceptives on the risk of hypertension and changes in blood pressure measures compared to non-HC and OC options.
    - Compared to non-HC users, there was no evidence of a difference in SBP with use of vaginal ring (−2.60 mmHg; 95%CI, −5.95, 0.75 mmHg) or transdermal patch (1.25mmHg; 95%CI -6.93, 4.43 mmHg)
    - Compared to non-HC users, there was evidence of a reduction in DBP with use of vaginal ring (−6.03 mmHg; 95%CI, −10.69, -1.36 mmHg) and no difference in DBP with transdermal patch (1.29mmHg; 95%CI -3.80, 6.38 mmHg)
- A systematic review of randomised trials from 2024 (4) examining an association between the use of OC (mostly COC) and the occurrence of systemic hypertension when compared to non-hormonal options.
    - The study found a significant increase in both SBP (p = 0.02) and DBP (p = 0.004) among users of cyclic oral contraceptives when compared to non-hormonal contraceptive options (values presented on a graph). The authors concluded that observed differences were not meaningful enough to merit any specific clinical recommendations.

Abbreviations: COC, combined oral contraception; CHC; combined hormonal contraception; DBP, diastolic blood pressure; OC, oral contraception; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

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4. Topic: Stroke

PICO							
Population 1	Women of reproductive age with a history of stroke (any type) (direct evidence)						
Population 2	Women of reproductive age (indirect evidence)						
Intervention	Hormonal contraception or copper intrauterine device						
Comparator	Other contraceptive method or no contraceptive method						
Outcomes 1	Recurrent stroke, other adverse events						
Outcomes 2	Ischaemic stroke, haemorrhagic stroke, cerebral vascular events						
Study design	Observational and interventional studies						
Preface	In the current version of the UK MEC, there is only a single heading for "stroke". The contraceptive methods risk profile is likely to differ by stroke's underlying pathology (arterial thrombotic/haemorrhagic/venous thrombotic events). A systematic search of medical literature (two databases, from inception to August 2024) returned two publications (1,2) with direct evidence (Population 1). However, as these are single case reports, they have not been included in the evidence profile. Owing to the lack of direct evidence, the table includes information from six studies (one systematic review (3) and five primary studies (4–8) with relevant indirect evidence of ischaemic and haemorrhagic stroke risk in the general population using hormonal contraception (Population 2), identified during the search for direct evidence. Two more recent studies (9) (10) were identified outside the main search.						
Outcome	**No. of studies, study design (number of participants)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Effect measure**	**Certainty of evidence**
Comparison: Combined hormonal contraception* vs no hormonal contraception							
Ischaemic stroke	10 observational studies (3)	Nonserious	Serious[a]	Serious[b]	Nonserious	Every 5-year increment of use OR 1.24 (95%CI 1.04, 1.49)	Very low

Haemorrhagic stroke	4 observational studies (3)	Nonserious	Nonserious	Serious[b]	Serious[c]	Every 5-year increment of use OR 1.13 (95%CI 0.93, 1.36)	Very low
Comparison: Combined hormonal contraception* (cessation) vs no hormonal contraception							
Ischaemic stroke	2 observational studies (3)	Nonserious	Nonserious	Serious[b]	Nonserious	Every 5-year increment from cessation OR 0.78 (95%CI 0.67, 0.92)	Very low
Haemorrhagic stroke	2 observational studies (3)	Nonserious	Nonserious	Serious[b]	Nonserious	Every 5-year increment from cessation OR 0.71 (95%CI 0.55, 0.92)	Very low
Comparison: Combined hormonal contraception vs combined hormonal contraception***							
Ischaemic stroke	2 observational studies (4,5)	Serious[d]	Nonserious	Serious[b]	Very serious[e]	IRR 1.2 (95%CI 0.41, 3.4) (5) OR 0.8 (95%CI 0.2, 4.5) (4)	Very low
Comparison: Progesterone-only pill vs no hormonal contraception							
Ischaemic stroke	3 observational studies (6,7,10)	Serious[f]	Nonserious	Serious[b]	Very serious[e]	aOR 0.9 (95%CI 0.4, 2.4) (6) aOR 2.8 (95%CI 0.4, 18.7)† (7) aIRR 1.6 (95%CI 1.2, 2.2) (10)	Very low

Comparison: Implant vs no hormonal contraception							
Ischaemic stroke	2 observational studies (8,10)	Serious[f]	N/A	Serious[b]	Very serious[e]	aRR 0.9 (95%CI 0.3, 2.7) aIRR 2.1 (95%CI 1.2, 3.8) (10)	Very low
Comparison: Levonorgestrel intrauterine device vs no hormonal contraception							
Ischaemic stroke	3 observational studies (8,9,10)	Nonserious	Nonserious	Serious[b]	Nonserious	aRR 0.70 (95%CI 0.50, 0.98) (8) aIRR 0.78 (95%CI 0.70, 0.88) (9) aIRR 1.10 (95%CI 1.00, 1.30) (10)	Very low
Intracerebral haemorrhage	1 observational study (9)	Nonserious	Not applicable	Serious[b]	Serious	aIRR 0.94 (95%CI 0.69, 1.28)	Very low

Abbreviations: a, adjusted; CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; RR, risk ratio.

*Combined oral contraception

**Patch

† Comparison with non-users of hormonal contraception without hypertension

Footnotes

a. Downgraded by one level for inconsistency ($I^2 = 85.9\%$).
b. Downgraded by one level for indirectness (general population not women with a history of stroke).
c. Downgraded by one level for imprecision (wide confidence intervals crossing line of no effect).
d. Downgraded by one level for risk of bias (the larger of two studies, a cohort, was assessed as of a fair quality).
e. Downgraded by two level for imprecision (very wide confidence intervals crossing line of no effect).
f. Downgraded by one level for risk of bias (study assessed as of a fair quality).

Additional considerations
The analysis of incidence risk ratio (IRR) of ischemic stroke by age group in the most recent retrospective cohort (4) of levonorgestrel intrauterine device (LNG-IUD) users, showed that the overall effect was probably driven by the decreased incidence rate of ischemic stroke in the oldest group of LNG-IUD users: LNG-IUD (40-49) vs non-users aIRR 0.75 (95%CI 0.66, 0.85). An Italian case-control study (11) with 31 female cerebral venous thrombosis cases and 93 healthy controls (type of oral contraception not defined) found that the use of oral contraception was more frequent among women with cerebral-vein thrombosis (96%) than among controls (32%) OR 22.1 (95%CI 5.9, 84.2). A Dutch case-control study (12) with 40 women (aged 18-54 years) with cerebral sinus thrombosis (cases) and 2,248 women (aged 18-49 years, controls) reported an age-adjusted OR of 13 (95%CI 5, 37) for the link between the use of oral contraception and cerebral venous thrombosis - 34/40 (85%) cases vs 1,007/2,248 (45%) of controls used oral contraception.

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5. Topic: Risk of venous thromboembolism (VTE)

5.1 Use of progestogen-only contraception in individuals at increased risk of VTE

PICO							
Population	Individuals of reproductive age with a personal characteristic or medical conditions known to increase risk of venous thromboembolism						
Intervention	Progestogen-only contraception						
Comparator	Alternative contraceptive method or no contraceptive method						
Outcomes	Venous thromboembolism (e.g. deep vein thromboembolism, pulmonary thromboembolism, cerebral sinus thrombosis)						
Study design	Observational and interventional studies						
Preface	A broad systematic search of medical literature on progestogen only methods and thrombosis risk (one database from 2016 to June 2023) returned 14 studies. The search was updated in February 2025 to cover the period between July 2023 and February 2025 and did not return any newer relevant studies. Of the studies identified, four (1–4) evaluated the risk of VTE in individuals of reproductive age with a personal characteristic or medical condition. One additional study older study with relevant data on the use of POP in SLE was included from Tepper et al. 2016 systematic review. (5) and one newer study (6) was not included as it reported a composite outcome of any thrombotic events where 67% of events captured in the study were arterial.						
Outcome	**No. of studies, study design (number of participants)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Effect measure**	**Certainty of evidence**
Comparison: Levonorgestrel intrauterine device vs no hormonal contraception in individuals with history of VTE (on anticoagulation treatment)							
Recurrent VTE	1 observational study (1) (NR)*	Very serious[a]	Not applicable	Nonserious	Very serious[b]	% of events per year LNG-IUS: 0 (95%CI 0.0, 24.0) No HC: 4.7 (95%CI 3.3, 6.4)	Very low
Comparison: Levonorgestrel intrauterine device vs no hormonal contraception in individuals with history of VTE (after switching from CHC)							
Recurrent VTE at 2 years	1 observational study (2) (56 participants)	Very serious[a]	Not applicable	Nonserious	Very serious[b]	Rate LNG-IUS: 1/19 (5.3%)	Very low

						No HC: 5/37 (13.5%)	
Comparison: Implant vs no hormonal contraception in individuals with history of VTE (after switching from CHC)							
Recurrent VTE at 2 years	1 observational study (2) (40 participants)	Very serious[a]	Not applicable	Nonserious	Very serious[b]	Rate Implant: 1/3 (33.3%) No HC: 5/37 (13.5%)	Very low
Comparison: Implant (immediate) vs no hormonal contraception in individuals during postpartum (< 4 weeks)							
Readmission for VTE within 30 days	1 observational study (3) (3,387, 120 participants)	Serious[c]	Not applicable	Nonserious	Very serious[d]	aOR 1.81 (95%CI 0.44, 7.45)[**]	Very low
Comparison: Progestogen-only pill vs no hormonal contraception in individuals with systemic lupus erythematosus							
PE	1 observational study (7) (33 participants)	Very serious[e]	Not applicable	Nonserious	Very serious[b]	Rate POP: 1/15 (6.7%) No HC: 1/18 (5.6%)	Very low
Comparison: Progestogen-only pill vs no hormonal contraception in individuals with history of VTE (after switching from CHC)							
Recurrent VTE at 2 years	1 observational study (2) (55 participants)	Very serious[a]	Not applicable	Nonserious	Very serious[b]	Rate POP: 1/18 (5.6%) No HC: 5/37 (13.5%)	Very low
Comparison: Depot medroxyprogesterone acetate (within 7 days) vs no hormonal contraception in individuals during postpartum (< 12 weeks)							
VTE	1 observational study (4) (3,113,170 participants)	Nonserious	Not applicable	Nonserious	Nonserious	aIRR 1.9 (95%CI 1.38, 2.72)[***]	Low
Comparison: Depot medroxyprogesterone acetate vs no hormonal contraception in individuals with history of VTE (after switching from CHC)							
Recurrent VTE at 2 years	1 observational study (2) (42 participants)	Very serious[a]	Not applicable	Nonserious	Very serious[b]	Rate DMPA: 0/5 No HC: 5/37 (13.5%)	Very low

* Number of participants using LNG-IUS was not reported in Martinelli study; the group not using hormonal contraception included 1413 participants. Maher 2022 included 39 individuals.

**Adjustment for age, insurance payer, hypertension, tobacco consumption, peripartum infection, and postpartum haemorrhage.

***Adjustment for age, pregnancy-related and chronic conditions.

Abbreviations: a, adjusted; CHC, combined hormonal contraception; DMPA, depot medroxyprogesterone acetate; HC, hormonal contraception; IRR, incidence rate ratio; LNG-IUS; levonorgestrel intrauterine system; OR, odds ratio; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

Footnotes

a. Downgraded by two levels for risk of bias (concern over uncontrolled confounding).
b. Downgraded by two levels for imprecision (wide confidence intervals, and low event rate).
c. Downgraded by one level for risk of bias (concern over uncontrolled confounding and short follow-up time).
d. Downgraded by two levels for imprecision (the sample size was small given rarity of the outcome, resulting in insufficient numbers to rule out a type II error).
e. Downgraded by two levels for risk of bias (study assessed as poor in Tepper 2016 review (5)).

Additional considerations

Risk of VTE in pregnancy

Thrombosis and thromboembolism was the leading cause of maternal death in the UK in 2021-23 during or up to six weeks after the end of pregnancy. (8) Absolute incidence of VTE in pregnancy and the puerperium in the UK is 107 per 100 000 person-years (95%CI 93, 122 per 100 000 person-years). (9) Many fatal antenatal VTE events occur in the first trimester. Consequently, appropriate prophylaxis for women with a history of VTE should start as early as possible. (10,11)

Risk of VTE and personal characteristics

High BMI is an important personal characteristic to be considered in the context of VTE risk. There is an increased risk of VTE with increasing BMI especially above 30kg/m^2. (12,13) The combinate risk attributed to high BMI and CHC puts individuals at high risk of VTE. (14)

Risk of VTE with DMPA use in general population

To date, five observational studies (four case-controls and one population-level cohort) evaluated the association between the use of DMPA compared to no use of HC and the risk of VTE. (15–19) The studies vary in age (1998 to 2025), size (sample size range from 1,180 to 1,397,235) and number of adjustment factors. The reported aOR of the risk of VTE with the use of DMPA compared to no-HC use was around 2.5 (aOR range from 2.2 to 3.0), indicative of a two-fold increase in odds of VTE with the use of DMPA. The most recently published population-wide cohort study from Denmark (19), consistently with the evidence from case-control studies, reported an increased incidence rate ratio of VTE for DMPA use compared to no use of HC; aIRR 5.7 (95%CI 3.5, 9.3)

Mechanism of progestogens influence on thrombotic processes

There is no clear mechanical explanation of how progestogens could be affecting coagulation (blood thickness, structure of vessel wall or blood flow). (20)

The US Medical Eligibility Criteria for Contraception Use 2024

Changes in the US MEC 2024 for POC methods across various conditions associated with increased risk of thrombosis are mainly for DMPA moving it to higher category (most frequently to category 3). (21)

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5.2 Personal characteristics and conditions linked to increased risk of VTE [supplementary evidence]

Additional evidence

High BMI

A systematic review with meta-analysis of observational studies examined an association between BMI and the risk of VTE and PE in general population (mixed sex). (1) The pooled results showed an association between BMI and risk of VTE in the obese participants compared to participants whose BMI was defined as normal BMI (HR 1.62, 95%CI 1.29, 2.04, I^2 = 95%).

Superficial venous thrombosis

Individuals with superficial venous thrombosis are at higher risk for venous thrombosis than the general population. (2) *[Evidence adopted from USMEC 2024]*

Inflammatory bowel disease (IBD)

Women with IBD are at higher risk of VTE than individuals unaffected by the condition. (3)

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5.3 Cancer type and risk of VTE [supplementary evidence search]

Topic: Association between developing a particular type of cancer and risk of venous thromboembolism

Method: scoping search in PubMed limited to most recent systematic reviews

Summary of findings

Any cancer type

A systematic review of literature with network meta-analysis (NMA)* where cancer types were treated as a network node examined the rates of VTE depending on cancer type while adjusting for baseline VTE risk in individual studies. (1) Thirty studies (18 cancer types, 3 948 752 individuals) with similar cancer populations and study methods reporting VTE occurring within 1 year of diagnosis informed the NMA. The study estimated that 3.1% of individuals experienced VTE within 1 year of diagnosis. Cancer-specific rates ranged from 0.7 to 7.4%. The NMA reported that that pancreatic cancer (absolute VTE rate 7.4%, CrI 5.4 to 10.1%), followed by brain cancer (6.4%, CrI 4.4 to 9.2%) and ovarian cancer (6.1%, CrI 4.3 to 8.5%), was associated with the highest risk of VTE. [NB: estimated absolute VTE rates for other relevant cancers are cervical 3.2% CrI 1.9 to 5.1; uterine 3.1% CrI 2.1 to 4.4%; and breast cancer 1.8% CrI 1.3 to 2.3)]. The relative rankings of VTE risk for certain cancers changed based on disease stage and/or receipt of chemotherapy or surgery. The findings of this review are somewhat consistent with the results reported by an older systematic review with meta-analysis (2) that estimated the incidence rate of VTE in individuals undergoing chemotherapy for range of cancer types. The cancer type with the highest crude incidence rate of VTE were pancreatic (28.5%), endometrial (11.6%), bladder (11.3%), renal (11.1%), and blood cancer (10%). Estimated crude incidence rate of VTE with ovarian cancer was 8.2% and cervical cancer 6.4%.

Ovarian cancer

A systematic review of literature with meta-analysis estimated the incidence of VTE in individuals with advanced ovarian cancer receiving neoadjuvant chemotherapy. (3) Eleven studies were included in this review where the incidence of VTE ranged from 0% to 18.9%. The pooled incidence rate of VTE was 10% (95%CI 7, 13). The incidence rate remained largely unchanged even after restricting the analysis to studies judged at low risk of bias (pooled incidence of 11%, 95%CI 9, 14). A systematic review with meta-analysis that estimated the prevalence of chemotherapy-associated VTE among the individuals with ovarian cancer (4) reported comparable pooled incidence rate of VTE 9% (95%CI, 6, 12).

A pooled incidence rate of VTE among individuals with ovarian clear cell carcinoma, the second most common subtype of epithelial ovarian cancers, was estimated at 21.3% (95%CI 17.4, 25.9) in a 2023 systematic review. (5)

Abbreviations: CI, confidence interval; CrI, Credibility Interval; VTE, venous thromboembolism.

*The study was sponsored by Bristol Myers Squibb and Pfizer.

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6 Topic: High risk Human Papillomavirus (HPV)

PICO							
Population	Individuals of reproductive age with cervical high-risk Human Papillomavirus and no other known medical conditions						
Intervention	Any hormonal contraception or copper intrauterine device						
Comparator	Alternative contraceptive method, No contraceptive method						
Outcomes	HR-HPV detection, HR-HPV acquisition, HR-HPV clearance, HR-HPV persistence, CIN 2/3 (also known as HSIL), cervical cancer						
Study design	Observational studies, systematic review						
Preface	In the current version of the UKMEC, there is no category for "High-risk Human papilloma virus (HPV)", only categories for "cervical ectropion", "cervical intraepithelial neoplasia (CIN)" and "cervical cancer". Since 2019, HPV primary screening offered in England as part of NHS National Cervical Screening Programme. A systematic search of medical literature (a single database, to November 2024) returned five publications (1-5) that met the eligibility criteria.						
Outcome	**No. of studies, study design (number of participants)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Effect measure***	**Certainty of evidence**
Comparison: Copper intrauterine device vs no hormonal contraception							
HR-HPV detection	1 observational study (10,431 participants) (1)	Serious[a]	Not applicable	Nonserious	Nonserious	aOR 1.01 (95%CI 0.81, 1.27)	Very Low
Comparison: Levonorgestrel intrauterine device vs no hormonal contraception							
HR-HPV detection	1 observational study (12,194 participants) (1)	Serious[a]	Not applicable	Nonserious	Nonserious	aOR 1.21 (95%CI 1.04, 1.41)	Very Low
Comparison: Levonorgestrel intrauterine device vs no hormonal contraception							
HR-HPV persistence at 1 year	1 observational study (7,778 participants) (2)	Nonserious	Not applicable	Nonserious	Nonserious	aOR 1.32 (95%CI 0.75, 2.27)	Low
Comparison: Levonorgestrel intrauterine device vs Copper intrauterine device							
HR-HPV acquisition	1 observational study (302 participants) (3)	Serious[a]	Not applicable	Nonserious	Very serious[b]	Rate	Very low

						LNG-IUD 2 (1.3%) Cu-IUD 8 (6.9%) p = 0.056	
HR-HPV persistence	1 observational study (302 participants) (3)	Serious[a]	Not applicable	Nonserious	Very serious[b]	Rate LNG-IUD 58% (95%CI 41.9, 74.1) Cu-IUD 30% (95%CI 13.6, 46.4) P = 0.02	Very Low
HR-HPV clearance	1 observational study (302 participants) (3)	Serious[a]	Not applicable	Nonserious	Very serious[b]	Rate LNG-IUD 42% (95%CI 25.6, 57.8) Cu-IUD 70% (95%CI 53.6, 86.4) P = 0.04	Very Low
Comparison: Depot medroxyprogesterone acetate (injectable) vs no hormonal contraception							
HR-HPV acquisition	1 observational study (1,256 participants) (4)	Serious[a]	Not applicable	Nonserious	Serious[c]	aOR 0.87 (95%CI 0.55, 1.35)	Very Low
HR-HPV clearance **Follow-up: 18 months**	1 observational study (1,256 participants) (4)	Serious[a]	Not applicable	Nonserious	Serious[c]	aHR 0.78 (95%CI 0.45, 1.37)	Very Low
HR-HPV detection	1 observational study (258 participants) (5)	Serious[a]	Not applicable	Nonserious	Very serious[b]	aOR 4.7 (95%CI 1.4, 15.8)*	Very low
Comparison: Combined hormonal contraception vs no hormonal contraception**							
HR-HPV acquisition	1 observational study (1,256 participants) (4)	Serious[a]	Not applicable	Nonserious	Serious[c]	aOR 1.22 (95%CI 0.81, 1.83)	Very Low

HR-HPV clearance **Follow-up: 18 months**	1 observational study (1,256 participants) (4)	Serious[a]	Not applicable	Nonserious	Serious[c]	aHR 0.58 (95%CI 0.37, 0.94)	Very Low
HR-HPV detection	1 observational study (258 participants) (5)	Serious[a]	Not applicable	Nonserious	Very serious[b]	aOR 1.6 (95%CI 0.7, 3.7)	Very low

* Evidence for depot medroxyprogesterone acetate used more than 1 year

**Evidence only for combined oral contraception

Abbreviations: a, adjusted; CI, confidence intervals; CU-IUD, copper intrauterine device; LNG-IUD, Levonorgestrel intrauterine device; OR, odds ration; HR, hazard ratio; HR-HPV, high-risk Human Papillomavirus

Footnotes

a. Downgraded one level due to risk of bias (observational study design or low-moderate study quality).
b. Downgraded two levels due to imprecision (study sample size below 1,000 participants).
c. Downgraded one level due to imprecision (study sample size below 5,000 participants).

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7 Topic: Breast conditions – BRCA carriers

PICO	
Population	Individuals with BRCA mutation
Intervention	Any Hormonal contraception
Comparator	No comparator or non-hormonal contraception (incl. coper intrauterine device)
Outcomes	Breast Cancer
Study design	Observational studies, systematic reviews
Preface	At the stage of topic scoping for the UK MEC update, work on updating the breast cancer guideline (1) was ongoing. Due to the emergence of new evidence, such as the Fitzpatrick et al. study (2), the steering group felt that any evidence on a link between the use of hormonal contraception and breast cancer should be included in the upcoming UK MEC update. As the breast cancer guideline (1) did not cover the population with BRCA mutations, an additional literature search has been carried out to identify relevant evidence on the link between the use of hormonal contraceptives and breast cancer risk among individuals with BRCA mutations.

Summary of identified evidence

A systematic scoping search identified three relevant systematic reviews (3-5) and an individual participant data meta-analysis of prospective observation studies (6) published within the last three years that examined the question of a link between breast cancer risk and the use of hormonal contraception in BRCA mutation carriers. Both Jahanfar 2024 (3) and van Bommel 2023 (5) reviews concluded that oral contraceptives, compared to no hormonal contraception, potentially increase breast cancer risk in BRCA carriers, with Cohen 2023 (4) concluding that most of the included studies indicated no association with BC risk. Important to note that both Jahanfar 2024 (3) and van Bommel 2023 (5) include more up-to-date literature (up to February 2022 in Jahanfar 2024) and provide a quantitative data synthesis.

The authors of van Bommel 2023 (5) review also examined the difference in the effect by the type of BRCA mutation (BRCA1 vs BRCA2). They found no significant differences in the impact by type of mutation. However, the most recent meta-analysis of individual participants data from four observational cohorts (6) with 3,882 BRCA1 and 1,509 BRCA2 carriers provides some evidence suggestive that the risk of BC is higher for BRCA1 mutation carriers compared to BRCA2: aHR 1.29 (95%CI 1.04, 1.60) vs aHR 1.07 (95%CI 0.73, 1.57), respectively.

Abbreviations: a, adjusted; BRCA, breast cancer mutation; HC, hormonal contraception; HR, hazard ratio COCP; combined oral contraception pill; OCP, oral contraception pill.

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8 Topic: Ovarian cancer

PICO	
Population	Individuals of reproductive age with or after ovarian cancer
Intervention	Any hormonal contraceptive method or copper intrauterine device
Comparator	Alternative contraceptive method, No contraceptive method
Outcomes	Safety outcomes
Study design	Observational and interventional studies
Preface	A systematic search of medical literature (two databases, from May 2021 to Sep 2024) returned no relevant studies for direct evidence. Relevant indirect evidence on the link between hormonal contraceptive methods or copper intrauterine device and the risk of ovarian cancer in a general population (reproductive age individuals) was identified in the literature search. A summary of the findings is presented in the additional considerations.

Additional considerations

Types of ovarian cancer and age

While less common than in the older age groups, cases of OC (data for England, 1985-2019) have been steadily increasing among individuals aged 0-49 years. (1) Epithelial ovarian cancer (EOC) is considered to be an age-related disease affecting predominantly postmenopausal individuals; however, it still may affect younger individuals. (2) Types of OC presenting in younger individuals are: low grade serous ovarian cancer (median age of diagnosis of 43–55 years, comprising < 10% of all EOC; malignant germ cell tumours (about 70% diagnosed under the age of 30); sex cord stromal tumours (7% of all OC, with 70% of patients diagnosed in stage I, reproductive age women who may be eligible for fertility sparing treatment). (3) More commonly occurring tumours in this age group other than EOC, are borderline ovarian tumours. (4)

European clinical guidelines

The joint BMS-BGCS guideline does not contra-indicate the use of HRT following treatment for epithelial ovarian cancer, highlighting that potential risks and benefits should be discussed with the individual. (4)

The guidelines of the French national college of obstetricians and gynaecologists concluded that the use of hormonal contraception after serous or mucinous borderline ovarian tumours (BOT) was not contraindicated. (5,6) The following recommendation is made in the most recent BGCS guidelines (7).

- ‘Hormonal contraception after serous or mucinous BOT is not contraindicated. (Grade C)

Hormonal contraception and the risk of ovarian cancer

A pooled analysis from five studies from the Ovarian Cancer Association Consortium (637 BRCA carriers and 4,289 noncarriers) reported an interaction risk ratio for use of OCP of 1.30 (95%CI 1.07, 1.60), suggestive that the protective effects of OCP may be reduced in BRCA carriers compared with noncarriers. (8)

Hormonal contraception and the risk of ovarian cancer in BRCA carriers

A systematic review of observational studies with meta-analysis included ten studies evaluating the link between OCP and the risk of ovarian cancer in BRCA1/2 carriers. (9) The synthesis of the data showed that the risk of ovarian cancer decreased with the use of OCP (type not specified) compared to no use. The magnitude of the decrease varied: for the hazard ratio, it was 38% (HR 0.62, 95%CI 0.52, 0.74; 2 studies, 10,981 women), and for the odds ratio, it was 51% (OR 0.49, 95%CI 0.38, 0.63; 8 studies, 10,390 women). The protective effect of OCP disappeared after its use was discontinued.

An international case-control study published in 2022 provided evidence on the link between non-oral hormonal contraception and the risk of ovarian cancer in premenopausal women with BRCA1/2 mutations. (10) The study found no evidence of decrease or increase of the ovarian cancer risk with the use of implant (OR 0.33, 95%CI 0.10, 1.02)*, injection (OR 0.14, 95%CI 0.02, 1.11)* or IUD (OR 0.86, 95%CI 0.39, 1.90)* compared to no use. The protective effect of the implant was observed in a mixed population of premenopausal and menopausal women (OR 0.30, 95%CI 0.12, 0.73)*.

*Multivariate odds ratio adjusted for adjusted for history of breastfeeding (ever/never), parity (ever/never).

Abbreviations: BGCS, British Gynaecological Cancer Society; BMS, British Menopause Society; BRCA, Brest Cancer gene; EOC, epithelial ovarian cancer; HR, hazard ratio; HRT, hormone replacement therapy; IUD, intrauterine device; OCP, oral contraceptive pill; OR, odds ratio.

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9 Topic: Sexually transmitted infections (STIs)

9.1 Herpes Simplex Virus (HSV)

PICO	
Population	Individuals of reproductive age with HSV
Intervention	Use of hormonal contraception or copper intrauterine device
Comparator	No use of contraception or alternative method
Outcomes	Health Outcomes/Prognosis
Study Design	Observational studies
Preface	In the UKMEC 2016, HSV is not specifically mentioned as its own category, and can be assumed to come under the "Other current STIs" category. For IUC insertion/continuation this is a category 2 and for all other methods this is category 1. A systematic search of medical literature (a single database, from inception to November 2024) demonstrated no direct evidence on the effect of contraception on the outcomes of those with HSV.
Additional considerations	
Micks 2019 (1): A prospective study which looked at the effects of hormonal contraception vs no- hormonal contraception on HSV-2 shedding and lesion frequency. It found no statistically significant difference in these outcomes between those using hormonal and non-hormonal contraception, but the study did not breakdown hormonal contraception into specific types.	
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9.2 Chlamydia (CT)

PICO	
Population	Individuals of reproductive age with CT
Intervention	Use of hormonal contraception or copper intrauterine device
Comparator	No use of contraception or alternative method
Outcomes	Health Outcomes/Prognosis
Study Design	Observational studies and systematic reviews

Preface	In the UKMEC 2016, current CT infection is split into asymptomatic and symptomatic. For symptomatic and asymptomatic current infection, the UKMEC category for IUC insertion is 4 and 3 respectively, and therefore generally contraindicated. It is a category 2 for continuation of IUC and is category 1 for every other contraceptive method. It was highlighted in the steering group discussion that the approaches in the UKMEC between CT & GC are different (no differentiation by symptoms for GC). A systematic search of medical literature (a single database, from inception to November 2024) revealed 2 papers with direct evidence relevant to the UKMEC (1, 2). Both studies contained small numbers but showed no cases of PID in patients who had an STI present at time of IUC insertion. Only one study (1) looked specifically at CT, with the other looking at patients with either CT or GC as one category. Neither of these studies comment on symptomatic versus asymptomatic status. As these studies are consistent with the current UKMEC, no grading of the evidence took place.

Additional Considerations

Jatlaoui 2016 (3): Systematic review assessing the risk of PID amongst women with current asymptomatic cervical infection or at high risk of STIs comparing those with an IUC in situ with those without. Included 2 studies with direct evidence and 8 with indirect. Authors concluded that limited evidence suggests that IUD placement does not increase the risk of PID compared with no IUD placement among women with asymptomatic undiagnosed cervical infection or at high risk of STIs.

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9.3 Gonorrhoea (GC)

PICO	
Population	Individuals of reproductive age with GC
Intervention	Use of hormonal contraception or copper intrauterine device
Comparator	No use of contraception or alternative method
Outcomes	Health Outcomes/Prognosis
Study Design	Observational and systematic reviews

Preface	In the UKMEC 2016, current GC is a category 4 for initiation of IUC, category 2 for continuation of IUC and a category 1 for all other hormonal methods of contraception. There is no differentiation between asymptomatic and symptomatic GC infection. A systematic search of medical literature (a single database, from inception to November 2024) demonstrated 3 papers (1-3) which gave direct evidence on the risk of Pelvic Inflammatory Disease in those with GC who were using hormonal contraception. The findings of newer studies are consistent with evidence presented in the UKMEC.

Additional considerations

Obafemi 2022 (4): Retrospective study which demonstrated that of 270 participants, 74% received same day IUD insertion with 9 subsequent cases of GC or CT identified (study does not differentiate between GC and CT) in same day insertion group. No cases of PID were identified at 30 days.

Drake 2015 (5): Retrospective study that demonstrated that of 283 participants who underwent LNG-IUS insertion that 0.7% (2) of these patients were diagnosed with PID within the next 12 months. One of those diagnosed with PID had a positive GC test from a screening test taken on the day of insertion. This study does not mention if this patient was symptomatic or not.

Mohllajee 2006 (6): Systematic review including 6 articles of indirect evidence comparing risk of PID in those with a Cu-IUD with and without an STI at time of insertion. All included studies found an increased risk of PID in those with an infection compared to those without an infection at time of insertion with crude relative risks ranging from 1.63 to 46.35. No differentiation was made between GC and CT.

Jatlaoui 2016 (7): Systematic review assessing the risk of PID amongst women with current asymptomatic cervical infection or at high risk of STIs comparing those with an IUC in situ with those without. Included 2 studies with direct evidence and 8 with indirect. Authors concluded that limited evidence suggests that IUD placement does not increase the risk of PID compared with no IUD placement among women with asymptomatic undiagnosed cervical infection or at high risk of STIs.

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9.4 Syphilis (STS)

PICO	
Population	Individuals of reproductive age with STS
Intervention	Use of hormonal contraception or copper intrauterine device
Comparator	No use of contraception or alternative method
Outcomes	Health Outcomes/Prognosis
Study design	Observational studies
Preface	At the UKMEC Steering Group it was discussed that the clinical picture with regards to STIs in general has changed e.g. the increasing discussion around Mycoplasma infections. It was therefore considered as to whether the addition of other specific STIs as standalone categories was required. A systematic search of medical literature (a single database, from inception to November 2024) revealed no evidence relevant to the effect of contraception on those with STS. Therefore, there is insufficient evidence to pursue STS inclusion in the UKMEC further.

9.5 Trichomonas Vaginalis (TV)

PICO	
Population	Individuals of reproductive age with TV
Intervention	Use of hormonal contraception or copper intrauterine device
Comparator	No use of contraception or alternative method
Outcomes	Health Outcomes/Prognosis
Study design	Observational studies
Preface	In the last iteration of the UKMEC in 2016, TV infection comes under the category “Vaginitis (Including Trichomonas Vaginalis and Bacterial Vaginosis) (current)”, with IUC methods being category 2 and all other methods of contraception being category 1. A systematic search of medical literature (two databases, from inception to November 2024) produced no direct evidence on the effect of contraception on outcomes in those individuals with TV. Three systematic reviews (1-3) were identified which contained indirect evidence on the effect of contraception use in individuals and their risk of TV acquisition. The general conclusion from each of these studies (detailed below) was that hormonal contraception did not increase risk of TV acquisition.
Additional considerations	

Atker 2022 (1): Systematic review and meta-analysis. 9 included studies looked at TV and only 6 of these studies included adjusted OR/RR. Of these 6 studies only 1 had a confidence interval which did not contain 1. This suggested that there was a 47% reduction the risk of incidence of TV in those using progestogen-only contraception. The study did not define type of progestogen only methods any further or refer to the different types. Deese 2018 (2): Systematic review which did not identify any Randomised Controlled Trials and consisted of poor-quality studies. Concluded that overall hormonal contraception did not increase the risk of TV acquisition. McCarthy 2019 (3): Systematic review. In included studies evidence was consistent that Depo medroxyprogesterone and oral contraceptive pills (did not break this down further) reduced risk of TV acquisition. Data on implants, injections and intrauterine contraception was limited and contradictory.
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9.6 Mycoplasma Genitalium (MG)

PICO	
Population	Individuals of reproductive age with MG
Intervention	Use of hormonal contraception or copper intrauterine device
Comparator	No use of contraception or alternative method
Outcomes	Health Outcomes/Prognosis
Study design	Observational and interventional studies
Preface	During the update of the FSRH IUC guideline in 2023 it was acknowledged that testing for and management of MG had become more widespread since the last update to the UKMEC in 2016 (1). It was generally considered that in the 2016 iteration of the UKMEC, MG came under the category of “Other Current STI’s (excluding HIV and Hepatitis)” for which IUC is considered category 2 and all other methods are category 1. Therefore, for this current UKMEC update it was decided that the CEU would look for evidence specifically regarding MG and contraceptive use and whether this has an adverse effect on health outcomes. A systematic search of medical literature (two databases, from inception to November 2024) yielded no relevant direct evidence regarding individuals with a MG infection and how use of contraception impacted the course of the infection or the risk of adverse

	outcomes e.g. PID. One study was found that contained indirect evidence, which demonstrated a non-statistically significant increase in incidence of MG in individuals using Norethisterone Enanthate injection (2).

Additional considerations

BASHH guideline from 2018 on MG (3) states that MG should not be screened for in asymptomatic cisgender women. Testing should be carried out on cisgender women who have signs and symptoms of PID. Testing should be considered in cisgender women with mucopurulent cervicitis, particularly post-coital bleeding. The guideline also acknowledges that most cisgender women with MG infection are asymptomatic. The US MEC (4) has no mention of MG specifically in its STI section.

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10 Topic: High risk of Human Immunodeficiency Virus (HIV)

PICO	
Population	Individuals of reproductive age at high risk of human immunodeficiency virus infection (seronegative)
Intervention	Any hormonal contraceptive method or copper intrauterine device
Comparator	Alternative contraceptive method, No contraceptive method
Outcomes	HIV acquisition, genital shedding, safety outcomes (death, any adverse event)
Study design	Interventional and observational studies
Preface	The 2016 UK MEC was amended to reflect the findings of the large multicentre, open-label randomised trial conducted in Africa (1). We conducted a systematic search of two databases (from January 2018 up to January 2025) to identify number of relevant studies evaluating the safety of contraceptive options (hormonal and copper intrauterine device) in the population of individuals at high risk of HIV infection. The search returned numerous relevant studies, including two randomised controlled trials (RCTs) (1,2), two systematic reviews (3,4), and one narrative review (5). The studies provide evidence predominantly for intramuscular depot medroxyprogesterone acetate, levonorgestrel implant (implant) and copper intrauterine device (Cu-IUD). In the presence of higher-quality evidence coming from randomised trials, we decided to present the evidence only from these studies. The captured systematic & narrative reviews provide a summary of observational data.

Outcome	No. of studies, study design (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Certainty of evidence
Comparison: Depot medroxyprogesterone acetate (injectable) vs Copper intrauterine device							
HIV acquisition	1 RCT (5,127 participants) (1)	Nonserious	Not applicable	Nonserious	Nonserious	HR 1.04 (96%CI 0.82, 1.33)*	High
Any serious adverse events	1 RCT (5,216 participants) (1)	Nonserious	Not applicable	Nonserious	Nonserious	RR 0.53 (95%CI 0.38, 0.75)	High
Death	1 RCT (5,216 participants) (1)	Nonserious	Not applicable	Nonserious	Serious[a]	RR 1.20 (95%CI 0.37, 3.92)	Moderate
Comparison: Depot medroxyprogesterone acetate (injectable) vs Implant							
HIV acquisition	1 RCT (5,144 participants) (1)	Nonserious	Not applicable	Nonserious	Nonserious	HR 1.23 (95%CI 0.95, 1.59)*	High

Any serious adverse events	1 RCT (5,522 participants) (1)	Nonserious	Not applicable	Nonserious	Nonserious	RR 0.63 (95%CI 0.44, 0.90)	High
Death	1 RCT (5,522 participants) (1)	Nonserious	Not applicable	Nonserious	Very serious[b]	RR 6.01 (95%CI 0.72, 49.88)	Low
Comparison: Copper intrauterine device vs Implant							
HIV acquisition	1 RCT (5,159 participants) (1)	Nonserious	Not applicable	Nonserious	Nonserious	HR 1.18 (96%CI 0.91, 1.53)*	High
Any serious adverse events	1 RCT (5,220 participants) (1)	Nonserious	Not applicable	Nonserious	Nonserious	RR 1.18 (95%CI 0.88, 1.59)	High
Death	1 RCT (5,220 participants) (1)	Nonserious	Not applicable	Nonserious	Very serious[b]	RR 5.01 (95%CI 0.59, 42.87)	Low

*Based on Kaplan-Meier curves for the primary, modified intention-to-treat analysis

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; RCT, randomised controlled trial; RR, risk ratio

Footnotes

a. Downgraded one level for imprecision (due to low event rate).
b. Downgraded one level for imprecision (due to very low event rate).

Additional considerations

United States and World Health Organization Medical Eligibility Criteria

The latest update of the United States Medical Eligibility Criteria (US MEC) for contraceptive use (2024)(6) included an update to the high risk of human immunodeficiency virus (HIV) infection category. This update was aligned with a review they published in 2020 (3), which updated previous recommendations to state that progestin-only injectable contraception (including depot medroxyprogesterone acetate) and intrauterine devices (including levonorgestrel and copper-bearing) are safe for use without restriction among women at high risk for HIV infection. The statement is also in line with the 2019 World Health Organization MEC guidance. (7)

Observational studies

An updated systematic review and synthesis of observational study on the association between depot medroxyprogesterone acetate and HIV acquisition (3) did not change previous conclusions (8) suggesting an increased risk of HIV acquisition with depot medroxyprogesterone acetate use. However, the data from the ECHO randomised controlled trial (1) presented in the evidence profile does not support such an association. The observational and randomised evidence for copper intrauterine device is consistent and indicates no increased risk of HIV acquisition with copper intrauterine device use. (4)

Effect on HIV susceptibility (mechanistic evidence)

Zalenskaya 2018 (9) identified gene expression changes in cervical epithelial cells following depot medroxyprogesterone acetate use, including pathways related to mucosal thinning, inflammation, and epithelial barrier disruption. These findings were based on cervical biopsies from healthy women before and after initiating depot medroxyprogesterone acetate.

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11 Topic: Liver disease

PICO	
Population	Individuals of reproductive age with liver disease
Intervention	Hormonal contraceptive methods
Comparator	Alternative hormonal contraceptive method or no hormonal contraception
Outcomes	Any safety outcomes
Study design	Observational and interventional studies
Preface	A systematic search of medical literature (two databases, from inception to May 2025) returned: • no relevant studies for conditions such as cholestasis, viral hepatitis, cirrhosis, liver tumours, deranged liver function tests, alcoholic liver disease, or Budd-Chiari syndrome, and • a single study in individuals with metabolic dysfunction associated steatotic liver disease (MASLD)* exposed to oral contraception of any type (8). The single study with MASLD individuals and relevant indirect evidence on the link between contraception use and liver disease in population without liver disease identified in the literature search are summarised below. **Formerly known as non-alcoholic fatty liver disease*

Additional considerations

Liver tumours

Two observational retrospective studies examined a link between the use of HC [CHC (9), and POC (10)] and the risk of developing hepatocellular adenoma (HCA). The first study included 183 individuals with diagnosis of HCA, of whom 132 had used CHC (all individuals stopped CHC at the point of diagnosis). The study found that weight loss was associated with disease regression ($p < 0.0001$) and exposure to oestrogen at baseline (score combining exposure from external source and internal secretion) predicted radiological regression of HCA (OR 2.33, 95%CI 1.29, 4.19). Use of COC >12 yrs as a standalone factor was not statistically significantly associated with HCA disease regression [complete or partial] (OR 1.72, 95%CI 0.56, 5.28) or progression (OR 0.76, 95%CI 0.20, 2.87), or transformation to HCC (OR 1.08, 95%CI 0.065, 17.97). (9) The study authors concluded that weight variation is strongly associated with radiological changes after discontinuation of OC.

The other study (10), a single-centre retrospective cohort including 34 individuals aged 16-45 with HCAs, examined tumour growth during a period of exposure to POC, exogenous oestrogen or no exogenous hormones. During the follow-up (median of 11 months), the percentage change in sum of adenoma diameters from baseline to last available scan was -15.0% with POC, 29.4% with oestrogen ($p = 0.04$), and -7.4% with no hormonal exposure.

Metabolic dysfunction Associated Steatotic Liver Disease (MASLD)

A cross-sectional study, including 160 pre-menopausal individuals, investigated the relationship between MASLD and gender, reproductive status, and use of OC. The study found evidence suggestive that use of OC was associated with an increased risk of lobular inflammation (ACOR 2.69, 95%CI 1.27, 5.84) and Mallory-Denk bodies (ACOR 3.02, 95%CI 1.29, 7.37) in pre-menopausal women. (8)

The findings of two studies examining the link between the use of HC and the odds of developing MASLD in individuals without liver disease are inconsistent. (11,12) A population-based cross-sectional study including 4,338 individuals aged 20-60 years found evidence suggestive that current use of OC is linked to a lower odds of MASLD compared to no use of HC (adjusted OR 0.50, 95%CI 0.26, 0.98). The effect estimate was adjusted for age, race/ethnicity, smoking status, history of diabetes or hypertension and education. However, a more recent nested case-control study (1861 cases and 17,664 controls) from the Multiethnic Cohort Study found evidence suggestive that use of OC was linked with an increased odds of MASLD (OR 1.14, 95%CI 1.01, 1.29). (12)

Abbreviations: ACOR, adjusted cumulative odds ratio; CHC, combined hormonal contraception; HCA, hepatocellular adenomas; HC, hormonal contraception; IUS, intrauterine system; MASLD, metabolic dysfunction associated steatotic liver disease; OC, oral contraceptives; OR, odds ratio; POC, progestogen-only contraception.

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12 Topic: Sickle cell disease and trait

12.1 Sickle cell disease

PICO							
Population	Individuals of reproductive age with sickle cell disease						
Intervention	Any hormonal or IUS contraception						
Comparator	Any other hormonal contraception or IUS or no hormonal contraception						
Outcomes	Any adverse events or complication						
Study design	Observational and interventional studies						
Preface	A systematic search of medical literature (two databases, from inception to July 2024) returned four relevant studies (one available as a doctoral thesis). (1–4) Additionally, we included six relevant studies (5–10) from a systematic review published in 2012. (11) Of these, two studies contained overlapping data and reported only biomarker data (6,7), and one study did not present any extractable data (5).						
Outcome	**No. of studies, study design (number of participants)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Effect measure**	**Certainty of evidence**
Comparison: Progesterone-only pill vs no hormonal contraception							
Thromboembolism†	1 observational study (271 participants) (1)	Nonserious	Not applicable	Nonserious	Serious[a]	aHR 1.64 (95%CI 0.89, 3.02)	Very low
Comparison: Progesterone-only pill vs levonorgestrel intrauterine device							
Thromboembolism†	1 observational study (1,160 participants) (2)	Nonserious	Not applicable	Nonserious	Serious[b]	aHR 0.38 (95%CI 0.13, 1.11)	Very low
Comparison: Implant vs Copper intrauterine device							
Thromboembolism†	1 observational study (1,094 participants) (2)	Nonserious	Not applicable	Nonserious	Serious[b]	aHR 1.00 (95%CI 0.46, 2.17)	Very low

Comparison: Depot medroxyprogesterone (injectable) vs placebo							
Bone pain during 30-week follow-up*	1 RCT (cross over) (23 participants) (10)	Serious[c]	Not applicable	Nonserious	Serious[d]	DMPA: 14/23 (61%) Placebo: 20/23 (87%)	Very low
Severity of painful crises	1 RCT (cross over) (23 participants) (10)	Serious[c]	Not applicable	Nonserious	Serious[d]	DMPA 2.0[§] Placebo 1.8[§]	Very low
Comparison: Depot medroxyprogesterone (injectable) vs levonorgestrel intrauterine device							
Thromboembolism[†]	1 observational study (3,136 participants) (2)	Nonserious	Not applicable	Nonserious	Serious[b]	aHR 0.67 (95%CI 0.40, 1.11)	Very low
Comparison: Depot medroxyprogesterone (injectable) vs progestogen-only pill							
Thromboembolism[‡]	1 observational study (56 participants) (9)	Very serious[e]	Not applicable	Nonserious	Very serious[f]	No events recorded	Very low
Increased crises	1 observational study (56 participants) (9)	Very serious[e]	Not applicable	Nonserious	Very serious[f]	No events recorded	Very low
Discontinuation due to adverse events	1 observational study (56 participants) (9)	Very serious[e]	Not applicable	Nonserious	Very serious[f]	RR 1.73 (95%CI 0.31, 9.57)	Very low
Irregular bleeding	1 observational study (56 participants) (9)	Very serious[e]	Not applicable	Nonserious	Very serious[f]	RR 1.54 (95%CI 0.61, 3.86)	Very low
Comparison: Combined hormonal contraception vs no hormonal contraception							
Thromboembolism[†]	3 observational studies (297 participants) (1,3,4)	Nonserious	Nonserious	Nonserious	Serious[a]	RR 0.99 (95%CI 0.52, 1.88)	Very low
Blood transfusion	2 observational studies (93 participants) (3,4)	Serious[g]	Nonserious	Nonserious	Very serious[f]	RR 1.16 (95%CI 0.77, 1.73)	Very low
Pulmonary hypertension	1 observational study (54 participants) (3)	Very serious[h]	Not applicable	Nonserious	Very serious[f]	RR 0.40 (95%CI 0.10, 1.56)	Very low
Arterial hypertension	1 observational study (54 participants) (3)	Very serious[h]	Not applicable	Nonserious	Very serious[f]	RR 0.36 (95%CI 0.07, 1.91)	Very low

Sickling crises	1 observational study (54 participants) (3)	Very serious[h]	Not applicable	Nonserious	Very serious[f]	RR 1.07 (95%CI 0.75, 1.54)	Very low
Severe sickle-cell crises	1 observational study (39 participants) (4)	Serious[i]	Not applicable	Nonserious	Very serious[f]	RR 0.33 (95%CI 0.05, 2.26)	Very low
Comparison: Combined hormonal contraceptive vs progestogen-only pill							
Thromboembolism†	2 observational studies (281 participants) (1,9)	Nonserious	Nonserious	Nonserious**	Serious[a]	RR 0.71 (95%CI 0.37, 1.34)	Very low
Increased crises	1 observational study (97 participants) (9)	Serious[c]	Not applicable	Nonserious**	Extremely serious[j]	RR 4.10 (95%CI 0.23, 73.88)	Very low
Discontinuation due to adverse events	1 observational study (97 participants) (9)	Serious[c]	Not applicable	Nonserious**	Very serious[f]	RR 1.79 (95%CI 0.40, 7.93)	Very low
Irregular bleeding	1 observational study (97 participants) (9)	Serious[c]	Not applicable	Nonserious**	Very serious[f]	RR 0.22 (95%CI 0.06, 0.84)	Very low
Comparison: Combined hormonal contraceptive vs Depot medroxyprogesterone (injectable)							
Painful crisis at 3 months	1 observational study (27 participants) (8)	Very serious[e]	Not applicable	Nonserious	Very serious[f]	Rate COC 72.5%*** DMPA 50%	Very low
Painful crisis at 12 months	1 observational study (27 participants) (8)	Very serious[e]	Not applicable	Nonserious	Very serious[f]	Rate COC 45.5%*** DMPA 30%	Very low
Adverse events	1 observational study (27 participants) (8)	Very serious[e]	Not applicable	Nonserious	Very serious[f]	No reported events	Very low

†Venous thromboembolism
‡ Deep venous thromboembolism
§mean
*In 2007 Cochrane review (12) the data from the study were incorrectly use to estimate the effect and reported as Odds Ratio of 0.23 (95%CI 0.05, 1.02)
**Evidence mainly for oral combined contraception
***Statistical significance not reported

Abbreviations: a, adjusted; CI, confidence interval; COC, combined oral contraceptive; DMPA, depo medroxyprogesterone hormonal contraception; HR, hazard ratio; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio.

Footnotes

a. Downgraded by one level for imprecision (study with more than 100 but less than 1000 participants, confidence interval crosses the line of no difference)
b. Downgraded by one level for imprecision (confidence interval crossing line of no difference)
c. Downgraded by one level for risk of bias (study assessed as of a fair quality in Haddad et al. 2012 systematic review (11))
d. Downgraded by one level for imprecision (study with less than 100)
e. Downgraded by two levels for risk of bias (study assessed as of a poor quality in Haddad et al. 2012 systematic review (11))
f. Downgraded by two levels for imprecision (study with less than 100 participants, no events or confidence interval crosses the line of no difference)
g. Downgraded by two levels for risk of bias (Eissa 2013 scored 6 and Carvalho 2017 4 points out of 9 on NOS scale)
h. Downgraded by two levels for risk of bias (Carvalho 2017 score only 4 points out of 9 on NOS scale)
i. Downgraded by one level for risk of bias (Eissa 2013 scored 6 points out of 9 on NOS scale)
j. Downgraded by three levels for imprecision (study with less than 100 participants, extremally wide confidence interval crosses the line of no difference)

NB Three studies included in Haddad et al. 2012 systematic review (Barbosa 2001, Nascimento 1998, Ladipo 1993) were not included in above table as they have evaluated safety of contraceptive method not used in the UK.

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12.2 Sickle cell trait

PICO	
Population	Individuals of reproductive age with sickle cell trait
Intervention	Any hormonal or IUS contraception
Comparator	Any other hormonal contraception or IUS or no hormonal contraception
Outcomes	Any adverse events or complication
Study design	Observational and interventional studies
Preface	A systematic search of medical literature (two databases, from inception to July 2024) returned a single relevant study (one available as a doctoral thesis). (1) Additionally, there was one older study (2) with relevant population included in the past systematic review (3). However, the contraceptive option in the older study was a mix of oral and non-oral contraceptives hence is of a limited utility to inform the UK MEC.
Additional considerations	
A single observational study reported on the safety of combined hormonal contraception compared to no hormonal contraception. (1) There was insufficient data to comment on any difference in the risk of thrombosis (venous or arterial), blood transfusion or increased sickle cell crises due to a lack of events. Very limited evidence (15 individuals in total, nine combined oral contraception users and seven no HC users) suggests a lower hospital admission rate with	

combined hormonal contraception compared to no hormonal contraception (0% vs 28.6%) with a higher rate of side effect (such as headache, nausea, mood swings, breast tenderness) with combined hormonal contraception use compared to no hormonal contraception (25% vs 0%).

Risk of VTE due to sickle cell trait

A systematic review (4) found the odds of VTE was 1.7 in individuals with sickle cell trait compared to individuals without the trait. The association was not seen in pregnant or postpartum populations.

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13 Topic: Chronic Kidney Disease

PICO	
Population	Individuals of reproductive age with chronic kidney disease
Intervention	Any hormonal contraceptive method or copper intrauterine device
Comparator	Alternative contraceptive method, No contraceptive method
Outcomes	Renal function (e.g. creatinine, GFR, electrolyte abnormalities, volume overload, metabolic acidosis), hypertension, anaemia, bone mineral density, cardiovascular disease, thrombosis, infection (including urinary tract infection, pelvic inflammatory disease), adverse events.
Study design	Observational and interventional studies
Preface	A systematic search of medical literature (two databases, from inception to July 2024) returned three studies reporting on the use of contraception in individuals with chronic kidney disease (1–3) of which one study is an evaluation of pharmacokinetics properties (3), and five studies with renal transplant patients (4–8). Data from Dicks et al. study (2) are not used in the below evidence profile as it is unclear whether the formulation in the study looked at combined oral contraceptive or a mix of progesterone only and combined oral contraceptives). Data from the pharmacokinetics study (3) (multiple-dose phases) are summarised in additional considerations.

Outcome	No. of studies, study design (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure*	Certainty of evidence
Comparison: Intrauterine hormonal device vs no comparator							
Colic pain	1 observational study (40 participants) (4)	Nonserious	Not applicable	Serious [a]	Very serious [b]	Rate 5/40 (13%)	Very Low
Recurrent urinary tract infection	1 observational study (40 participants) (4)	Nonserious	Not applicable	Serious [a]	Very serious [b]	Rate 2/40 (5%)	Very Low
Pelvic infection	1 observational study (23 participants) (6)	Nonserious	Not applicable	Serious [a]	Very serious [b]	Rate 0/23	Very Low
Discontinuation	1 observational study (23 participants) (6)	Nonserious	Not applicable	Serious [a]	Very serious [b]	Rate 8/23 (34.8%)	Very Low

Discontinuation due to pelvic infection	1 observational study (11 participants) (7)	Very Serious [c]	Not applicable	Very Serious [d]	Very serious [b]	Rate 0/11	Very Low
IUD expulsion	2 observational studies (63 participants) (4,6)	Nonserious	Nonserious	Serious [a]	Very serious [b]	Rate range 8.7% (2/23) - 10% (4/40)	Very Low
Comparison: Progesterone only pill vs no comparator							
Hyperkalaemia	1 observational study (17 participants) (1)	Nonserious**	Not applicable	Nonserious	Very serious [b]	Rate 0/17	Very Low
Serum potassium	1 observational study (17 participants) (1)	Nonserious**	Not applicable	Nonserious	Very serious [b]	Serum potassium levels <5.5 mmol/L for all subjects (at drospirenone steady state)	Very Low
Comparison: Combined oral contraceptive (ethinyl estradiol with 3rd generation progestogen) vs no comparator							
Creatinine (mg/dL)	1 observational study (26 participants) (8)	Serious[e]	Not applicable	Serious [a]	Very serious [b]	Baseline 1.31±0.42 At 6 months 1.58±0.49	Very Low
Blood pressure	1 observational study (26 participants) (8)	Serious[e]	Not applicable	Serious [a]	Very serious [b]	Baseline 99.8±0.75 18 months 97.6±1.23	Very Low
Discontinuation	1 observational study (26 participants) (8)	Serious[e]	Not applicable	Serious [a]	Very serious [b]	Rate 2/36	Very Low
Comparison: Patch (ethinyl estradiol with norelgestromin) vs no comparator							
Creatinine (mg/dL)	1 observational study (10 participants) (8)	Serious[e]	Not applicable	Serious [a]	Very serious [b]	Baseline 1.35±0.32	Very Low

						At 6 months 1.49 ±0.39	
Blood pressure	1 observational study (10 participants)(8)	Serious[e]	Not applicable	Serious [a]	Very serious [b]	Baseline 94.7±1.25 At 18 months 97.7±0.75	Very Low
Discontinuation	1 observational study (10 participants) (8)	Serious[e]	Not applicable	Serious [a]	Very serious [b]	Rate 0/10	Very Low
Comparison: Depot medroxyprogesterone (injectable) vs no hormonal contraception (condom)							
Creatinine (mg/dL)	1 observational study (50 participants) (5)	Nonserious	Not applicable	Serious [a]	Very serious [b]	DMPA 1.36±0.55 Condom 1.36±0.64	Very Low

Abbreviations: DMPA, Depot medroxyprogesterone acetate.

*Continuous values are presented as mean ± standard deviation, unless stated otherwise

**Study funded by the pharmaceutical company

Footnotes

a. Downgraded by one level for indirectness (renal transplant recipients)
b. Downgraded by two levels for imprecision (study with less than 100 participants)
c. Downgraded by two levels for risk of bias (retrospective chart review scoring 4 out of 12 points on CASP checklist)
d. Downgraded by two levels for indirectness (renal transplant recipients where 64% used intrauterine device to manage menorrhagia)
e. Downgraded by one level for risk of bias (study quality assessed as poor in Paulen et al. 2010 systematic review (9))

Additional considerations

It is important that patients with CKD are using effective contraception as neonatal and maternal morbidity and mortality is higher in women with CKD. (10,11)

All severities of kidney disease appear to be associated with the increased risk of venous thromboembolism. The risk of venous thromboembolism associated with mild to moderate kidney disease is 1.3–2-fold increased. (12)

The pharmacokinetics study (3) of combined hormonal pill (ethinyl estradiol [EE] and norethindrone] in peritoneal dialysis patients and normal women found no difference in the pharmacokinetic parameters for norethindrone between both groups. In the multiple dosing part of the study the authors observed a greater difference in the area under the concentration curve 0-24 hr for EE in peritoneal dialysis patients compared with normal women: 1930.2 ±641.2 vs

1071.4±199.9 (pg/ml*hr). There was also a significant difference in the oral clearance for EE; 296.1±90.9 vs 525.8±91.8 (ml/hr*kg). The findings should be treated with caution due to inadequate sampling and general small study size (5 individuals in both groups).

The UK Renal Association, in their **2019** clinical practice guidelines on pregnancy and renal disease (11), recommends the progesterone-only pill, a progesterone subdermal implant, or the **progesterone intra-uterine system** as safe and effective options for women with CKD (Recommendation 3.1.3). Progesterone-only options are preferred over combined formulation due to the increased risk of hypertension and venous thromboembolism associated with the oestrogen component of the combined pill, risks particularly relevant for women with CKD with co-existing chronic hypertension and those known to be at increased risk of vascular disease, venous thromboembolism (due to anti-phospholipid antibodies or nephrotic syndrome), or cervical neoplasia in the context of immunosuppression.

The US MEC 2024 (13) introduced CKD as the condition is associated with increased risk for pregnancy-associated adverse health events. (5) The categorisation is based on evidence from three studies (1-3). The CKD category in the US MEC 2024 included four subcategories:

- **Current nephrotic syndrome**: category 2 for LNG-IUD (initiation & continuation), implant, progesterone only pill (excluding drospirenone for individuals with known hyperkalaemia); **category 3:** DMPA; category 4 for combined hormonal contraception and drospirenone for individuals with known hyperkalaemia)
- **Haemodialysis**: **category 2**: LNG-IUD (initiation & continuation), implant, progesterone only pill (excluding drospirenone for individuals with known hyperkalaemia); **category 3**: DMPA; **category 4:** combined hormonal contraception and drospirenone for individuals with known hyperkalaemia)
- **Peritoneal dialysis**: **category 2:** Cu-IUD initiation; LNG-IUD (initiation & continuation), implant, progesterone only pill (excluding drospirenone for individuals with known hyperkalaemia); **category 3**: DMPA; **category 4**: combined hormonal contraception and drospirenone for individuals with known hyperkalaemia)

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14 Topic: Osteoporosis and osteopenia

PICO	
Population	Individuals of reproductive age with osteoporosis or osteopenia (direct evidence) Individuals of reproductive age taking hormonal contraceptives (indirect evidence)
Intervention	Hormonal contraception or copper intrauterine device
Comparator	Alternative contraceptive method, No contraceptive method
Outcomes	Fracture, bone mineral density change
Study design	Observational and interventional studies
Preface	The FSRH guidelines mention BMD and fracture risk are associated with various forms of contraception, summarised below: • Combined hormonal contraception (2019): no clear negative impact on bone mineral density overall, but BMD accrual may be lower in adolescents using combined pill. • Intrauterine contraception (2023): no significant impact on BMD • Progestogen-only pill (2022): no evidence available • Progestogen-only implant (2021): insufficient evidence available to determine risk • Progestogen-only injectables (2014): progestogen-only injectable use is associated with a small loss of bone mineral density, which is usually recovered after discontinuation. A systematic search of two databases to May 2024 identified a range of studies relating to BMD and fracture risk in women with current or past use of hormonal contraception, published since the various FSRH guidelines. There was very limited direct evidence available for current users of hormonal contraception who have osteoporosis or osteopenia, so this table also presents the indirect evidence for changes in BMD and fracture risk for women of reproductive age who are using hormonal contraception, compared with those not using that form of contraception or (using a different specified form).
Context	The evidence for this topic was reviewed by the guideline development group who concluded that available evidence is insufficient to merit osteoporosis as a separate MEC category. However, the GDG members agreed that clarification on the impact of hormonal contraception on bone health should be highlighted in the relevant areas of the UKMEC. The section below contains the summary of most relevant studies on the impact of hormonal contraception on bone health.
Summary of evidence	
Levonorgestrel intrauterine system A single study reported on the fracture risk between LNG-IUS users and non-users of HC. (1) The evidence suggests no increased rate of fractures in users of LNG-IUD compared to non-users of HC (OR 0.99, 95%CI 0.81, 1.21).	

Depo medroxyprogesterone acetate (injectable)

A single study reported on the fracture risk between DMPA users and non-users of HC. (1) The study showed a potential increased fracture risk in DMPA users (more than 3 prescriptions) compared to non-users of HC [3-9 prescriptions aOR 2.4, (95%CI 1.42, 4.08); ≥10 prescriptions aOR 1.46, 95%CI 0.96, 2.23]. The effect seemed to reduce after DMPA cessation [1-2 prescriptions aOR 0.96, 95%CI 0.73, 1.26; 3-9 prescriptions aOR 1.14, 95%CI 0.86, 1.51] with the exception of long-term DMPA use [>10 prescriptions aOR 1.55, 95%CI 1.07, 2.27].

Progestogen-only pill

A single study reported on the fracture risk between POP users and non-users of HC. (2) The evidence suggests no increased risk of fractures in users of POP compared to non-users HC [OR 0.98, 95%CI 0.90, 1.07].

Combined hormonal contraception

Two studies from a relevant systematic review (3) reported on the fracture risk among users of CHC and non-users of HC. There was evidence suggestive of an increased risk of fractures in users of CHC vs non-users of HC (aRR 1.20; 95%CI 1.1, 1.4). In the postmenopausal population, three studies reported on the osteoporosis (4), osteopenia (4) and fracture risk (5,6) among the COC users compared to non-users of HC. The evidence suggests no increased risk of osteoporosis [aOR 1.27, 95%CI 0.82, 1.98] or fractures [aOR 1.01, 95%CI 0.85, 1.21 (5); aHR 0.96, 95%CI 0.91, 1.0 (7)] in users of COC. Evidence suggests a reduced risk of osteopenia in users of COC [aOR 0.71, 95%CI 0.59, 0.86] compared to non-users of HC.

Effect of HC on BMD

The evidence of the effect of contraceptive methods on BMD is variable: the impact of CHC reported in the literature is inconsistent (3,8,9) while DMPA users seem to have small but significantly lower BMD (10–12). In postmenopausal individuals, there is some evidence indicative of higher BMD (lumbar spine) with previous COC use. (4)

Abbreviations: a, adjusted; BMD, bone mineral density; CI, confidence interval; CHC, combined hormonal contraception; COC, combined oral contraception; DMPA, depot medroxyprogesterone acetate; DSG, desogestrel; DRSP, drospirenone; EE, ethinylestradiol; HC, hormonal contraception; HR, hazard ratio; IQR, interquartile range; MD, mean difference; OR, odds ratio; POP, progestogen-only pill; RR, risk ratio.

Additional considerations

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15 Topic: Multiple sclerosis

PICO	
Population	Individuals of reproductive age with multiple sclerosis (MS)
Intervention	Hormonal contraception or copper IUD
Comparator	Alternative contraceptive method, No contraceptive method
Outcomes	MS progression or relapse, VTE, BMD, other adverse outcomes
Study design	Observational and interventional studies
Preface	A systematic search of two databases (from inception to July 2024) identified one systematic review (1), on which the USMEC ratings were based, and three observational studies (2,3,4) published since the search date of the systematic review. • The systematic review (1) included two studies with unspecified oral contraceptives (OC) and two studies of combined oral contraceptives (COC). • One observational study (2) compared cyclic OC (unspecified) vs continuous OC (unspecified) vs no OC. • One longitudinal observational study (3) compared continuous vs cyclic COC. This is not included within the evidence profile but is summarised below under Additional Information. • One cohort study (4) compared prior vs current vs never use of OC (most commonly COC). Adverse events were only reported as an outcome by one study within the systematic review.

Outcome	No. of studies, study design (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Certainty of evidence
Comparison: Combined hormonal contraception† vs no hormonal contraception							
MS progression	1 systematic review (2 studies) (1)	Nonserious	Not applicable	Not serious	Serious[a]	Gava 2014 study Significantly lower probability of progression to SPMS in COC users (before and after onset) vs never users (p = 0.015) and COC users (only after	Very low

						onset) vs never users (p = 0.008) Pozzilli 2015 study HR 1.36 (95%CI 0.72, 2.58)	
Disability (measured using EDSS)	1 systematic review (1 study) (1)	Nonserious	Not applicable	Not serious	Serious[a]	Gava 2014 study‡ CHC: 2.3±1.6 no HC: 3.4±2.2 p < 0.05	Very low
Relapse rates (week 0 to 96)	1 systematic review (1 study) (1)	Nonserious	Not applicable	Not serious	Serious[a]	Pozzilli 2015 study‡ CHC: 0.44±0.09 No HC: 0.33±0.08	Very low
Comparison: Combined hormonal contraception (past use) vs no hormonal contraception							
Relapse rates	1 cohort study (162 participants) (4)	Nonserious	Not applicable	Serious[b]	Serious[a]	RR 0.64§ p = 0.031	Very low
Discontinuation due to adverse events	1 systematic review (1 RCT) (1)	Nonserious	Not applicable	Not serious	Serious[a]	Rate was similar between groups after MS onset groups.	Very low
Comparison: Oral contraception (type unspecified) vs no hormonal contraception							
MS progression	1 systematic review (2 studies) (1)	Serious[c]	Not applicable	Not serious	Serious[a]	Poser 1979/1982 study No difference between groups (p > 0.05) Sena 2012 study OC users after onset had significantly (p < 0.05) lower EDSS and MSSS values	Very low

						vs. never users after adjustment for age at DO, disease duration, smoking status and age at menarche.	
Benign course of disease (MSSS<2.5)	1 systematic review (1 study) (1)	Serious[c]	Not applicable	Not serious	Serious[a]	Sena 2012 study aOR 2.97 (95%CI 1.24, 6.54)	
Symptom scores (variability across cycles using Sympto MScreen*) ‡	1 observational study (47 participants) (2)	Serious[d]	Not applicable	Serious[e]	Very serious[f]	OC**: 1.22±0.47 No OC: 2.14±1.15 p = 0.000	Very low
Fatigue (variability across cycles using MFIS) ‡	1 observational study (47 participants) (2)	Serious[d]	Not applicable	Serious[e]	Very serious[f]	OC**: 3.44±1.68 No OC: 4.24±1.8 p = 0.01	

† Only combined oral contraception (data reported for lower dose of ethinyl estradiol)

‡ mean ± SD

§ majority of participants used combined oral contraception but some may have been on progestogen-only pill

*SymptoMScreen is a battery of 7-point Likert scales for 12 distinct domains commonly affected by MS: mobility, dexterity, body pain, sensation, bladder function, fatigue, vision, dizziness, cognition, depression, and anxiety.

**data for continuous use of oral contraception.

Abbreviations: a, adjusted; CI, confidence interval; CHC, combined hormonal contraception; COC, combined oral contraception; EDSS, Expanded Disability Status Scale; HC, hormonal contraception; HR, hazard ratio; OC, oral contraception; OR odds ratio; RCT, randomised controlled trial; MFIS, Modified Fatigue Impact Scale; MSSS, Multiple Sclerosis Severity Score; MS, multiple sclerosis; SPMS, Secondary Progressive Multiple Sclerosis.

Footnotes

a. Downgraded by one level for imprecision: small sample size (n < 1000 but > 100)
b. Downgraded by one level for indirectness: study included women with CIS or MS who initiated injectable DMT within two years of symptom onset, which may limit generalisability.
c. Downgraded by one level for risk of bias. Studies' risk of bias rated as poor or fair within the systematic review.

d. Downgraded by one level for risk of bias: only 47/70 eligible people included (study excluded those with < 4 weeks data or who were lost to follow-up). No information on type of oral contraceptive type or length of use, and no adjustment for age.
e. Downgraded by one level for indirectness: study included women with CIS or MS.
f. Downgraded by two levels for imprecision: very small sample size (n<100)

Additional considerations

The USMEC includes MS, based on evidence from 2016 systematic review (1).

- MS with prolonged immobility: IUC/IMP/POP = 1, DMPA = 2, CHC = 3
- MS without prolonged immobility: IUC/IMP/POP/CHC = 1, DMPA = 2

Evidence informing the decision: Limited evidence demonstrates that use of COCs or oral contraceptives (type not specified) among women with multiple sclerosis does not worsen the clinical course of disease.

Justification: Individuals with multiple sclerosis might have compromised bone health from disease-related disability, immobility, and use of corticosteroids. Use of DMPA, which has been associated with small changes in BMD, might be of concern.

Evidence: Limited evidence suggests that use of COCs or oral contraceptives (type not specified) among women with multiple sclerosis does not worsen the clinical course of disease.

Comment: No data exist that evaluate the increased risk for VTE among persons with multiple sclerosis using CHCs. However, persons with multiple sclerosis are at higher risk for VTE than those without multiple sclerosis.

Additional study/outcomes

- A longitudinal observational pilot study (3) including 19 individuals with relapsing multiple sclerosis matched to controls and compared continuous vs cyclic combined oral contraceptives. The study found no difference in time to relapse (p = 0.50) between continuous and cycling oral contraception users. Continuous oral contraception users showed a statistical trend to longer time to T2 lesion formation (p = 0.09) and longer time to contrast-enhancing lesion formation (p = 0.05). In 28 patients with at least a year of observation, there was a significant difference in time to T2 lesion formation (p = 0.03) and time to contrast-enhancing lesion formation (p = 0.02) between continuous and cycling OC users.
- A single cohort study (4) with 162 individuals reported slightly higher increase in EDSS over 8.5 years in those who had never used oral contraception compared with past or current use. The difference was not significant (p = 0.28).
- **Fracture risk:** the 2016 systematic review mentions that they found no evidence for the theoretical concern that progestogen-only injectables may be associated with BMD and fracture risk in the women with MS. Zapata et al. (1) cite a paper that compared the risk of fracture in patients with MS against healthy controls using data from the UK General Practice Research Database (5). The study reported that:
  - The median 5-year risk of osteoporotic facture is 1.6% for females aged 18–49 years with MS specifically.
  - Compared with controls, MS patients have a 1.2-fold increased risk of any fracture after adjustment, with higher risk for hip fracture (aHR 2.79, CI 1.83 to 4.26) and osteoporotic fracture (of the radius/ulna, vertebrae, femur, hip, humerus, pelvis or ribs): aHR 1.35 (CI 1.13 to 1.62).

- The HR was adjusted for age, sex, use of oral/intravenous glucocorticoids, antidepressants, hypnotics/anxiolytics, anticonvulsants in the previous 6 months, history of falling at index date, history of fracture at index date, history of smoking.
- For 'any fracture' HR was additionally adjusted for use of opioids in the previous 6 months, history of cerebrovascular disease and epilepsy.
- For hip fracture, HR was additionally adjusted for use of opioids in the previous 6 months, history of fatigue in the previous 6 months and BMI.
- For osteoporotic fracture, it was additionally adjusted for use of opioids in the previous 6 months, history of cerebrovascular disease, epilepsy and BMI.

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16 Topic: Progestogen-only pill – Drospirenone

PICO	
Population	Individuals of reproductive age and with special characteristics of interest
Intervention	Drospirenone only pill (4mg daily for 24 days – 4 placebo pills)
Comparator	Other progesterone-only pill or no contraception
Outcomes	Any safety outcome (e.g. thrombotic events, cardiovascular events, etc.)
Study design	Observational and interventional studies
Preface	A systematic search of medical literature (two databases, from inception to July 2024) returned five relevant studies (one published as a conference abstract) (1–5). One more study (6) was identified outside the main search. Of these three are secondary analyses of clinical trials with a broader (general) population (1–3), two single arm clinical trials (4,5), and one retrospective observational study (6).

Outcome	No. of studies, study design (number of participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Certainty of evidence
Population: individuals age ≥ 40 years old							
Thromboembolic or cardiovascular events	1 observational study (44 participants) (1)	Not possible to assess*	Not applicable	Nonserious	Very serious [a]	Rate 0/44	Very Low
Hyperkalaemia	1 observational study (44 participants) (1)	Not possible to assess*	Not applicable	Nonserious	Very serious [a]	Rate 0/44	Very Low
Discontinuation due to adverse events	1 observational study (44 participants) (1)	Not possible to assess*	Not applicable	Nonserious	Very serious [a]	Rate 5/44 (11.4%)	Very Low
Population: Body Mass Index ≥30 kg/m2							
Thromboembolic or cardiovascular events	3 observational studies (425 participants) (2)	Nonserious*	Nonserious	Nonserious	Serious [b]	Rate 0/425	Very Low
Population: at least one risk factor for venous thromboembolism							

Thromboembolic or cardiovascular events	3 observational studies (683 participants) (3)	Nonserious*	Nonserious	Nonserious	Serious [b]	Rate 0/683	Very Low
Population: **breastfeeding**							
Any Adverse Events	1 observational study (100 participants) (6)	Nonserious*	Not applicable	Nonserious	Serious [b]	Rate 6/100 (6%) **	Very Low
Serious Adverse Events	1 observational study (12 participants) (4)	Nonserious*	Not applicable	Nonserious	Very serious [a]	Rate 0/12	Very Low
Population: mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min)							
Hyperkalaemia	1 observational study (17 participants) (5)	Nonserious*	Not applicable	Nonserious	Very serious [a]	Rate 0/17	Very Low
Serum potassium	1 observational study (17 participants) (5)	Nonserious*	Not applicable	Serious [d]	Nonserious	Serum potassium levels <5.5 mmol/L for all subjects (drospirenone steady state)	Very Low

* Study funded by the pharmaceutical company
**All classified as mild and were transient

Footnotes

a. Downgraded by two levels for imprecision (study with less than 100 participants)
b. Downgraded by one level for imprecision (study with more than 100 but less than 1000 participants)
c. Downgraded by two levels for imprecision (study with less than 100 participants, wide range of drospirenone concentration values)
d. Downgraded by one level due to indirectness (drospirenone dose 3 mg)

Additional considerations

The evidence for the individuals with an increased risk of thrombotic events comes predominantly from a subgroup analysis of the clinical trials evaluating efficacy and safety of drospirenone-only oral contraception. (7–9) The safety data for these subgroups seems consistent with the findings from the general population - namely, there were no thrombotic or serious adverse events. Hyperkalaemia of 0.5% was reported in a single-arm clinical trial conducted in USA. (8) Overall, we identified ten publications reporting on the efficacy and safety of drospirenone-only pill in the general population. All studies were funded by the pharmaceutical industry.

A recent analysis of European pharmacovigilance data of individual reports of adverse events occurring while on combined contraceptives found a lower reporting of venous thromboembolism events with combined contraceptives, including natural oestrogens, compared to ethinylestradiol-containing pills. (10) The study also reported on the rate of thrombotic events with drospirenone-only formulation. The reported rate of thrombotic events to all reported adverse events for drospirenone only pill was 0.07 (92/1,361), which was similar to the value for estetrol/drospirenone combination (34/507) and distinctively lower than the rate reported for synthetic oestrogen and levonorgestrel combination (0.28; 3,869/13,583). The findings of this study have a hypothesis-generating nature and cannot be extrapolated to drive a definitive conclusion regarding the safety of investigated formulations.

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17 Topic: Combined Hormonal Contraception – Estetrol with Drospirenone

PICO							
Population	Individuals of reproductive age and with special characteristics of interest						
Intervention	Estetrol with drospirenone						
Comparator	Other progesterone-only pill or no contraception						
Outcomes	Any safety outcome (e.g. thrombotic events, cardiovascular events, etc.)						
Study design	Observational and interventional studies						
Preface	A systematic search of medical literature (two databases, from inception to July 2024) returned one publication with relevant data. (1) One more study (2) was identified outside the main search. In both cases relevant data came from subgroup analyses of clinical trials that included broader (general) populations. (1)						
Outcome	**No. of studies, study design (number of participants)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Effect measure**	**Certainty of evidence**
Population: **Body Mass Index ≥30 kg/m2**							
Thromboembolic events	1 observational study (337 participants) (1)	Nonserious*	Not applicable	Nonserious**	Serious[a]	Rate 0/337	Very Low
Adverse events	1 observational study (418 participants) (2)	Not possible to assess*	Not applicable	Nonserious**	Serious[a]	Rate 234/418 (56%)	Very Low
Serious adverse events	1 observational study (418 participants) (2)	Not possible to assess*	Not applicable	Nonserious**	Serious[a]	Rate 1/418 (0.2%)	Very Low
Discontinuation due to adverse events	1 observational study (418 participants) (2)	Not possible to assess*	Not applicable	Nonserious**	Serious[a]	Rate 1/418 (9.6%)	Very Low
*Study funded by pharmaceutical company **Evidence for formulation 15mg estetrol/3mg drospirenone							
Footnote a. Downgraded by one level for imprecision (study with more than 100 but less than 1000 participants)							

Additional considerations

Overall, ten publications were identified reporting on the efficacy and safety of estetrol (E4) with drospirenone combined pill in the general population.

Safety in the E4 with drospirenone arms across the studies

- Single study reported on two cases (2/1,864) of significantly elevated potassium levels (> 5nmol/l).(1)
- Serious AE reported in two studies with no events in one (111 individuals) (3) and a rate of 0.8% in another (1,553 individuals) (4).
- One study reported on severe AE 7.3% (3/41) (5).

Studies comparing E4 with drospirenone with other combined formulations predominantly focused on changes in biomarkers levels.

Safety of the E4 with drospirenone compared to other combine pills:

- After 6 cycles of treatment, all thrombin generation parameters are statistically less affected by E4 with drospirenone than ethinylestradiol-containing pills (drospirenone or levonorgestrel). (6)
- The rate of adverse events between two formulations with drospirenone (one with ethinylestradiol and the other with E4) was higher with E4 component (11/41 vs 4/41), but the discontinuation rate due to adverse events was comparable between the two groups. (5)
- A single study reported on two cases of hot flushes with E4 (5mg) with drospirenone compared to none in another evaluated formulations (higher dose sterol with drospirenone, ethinylestradiol with drospirenone, and E4 with levonorgestrel) (3)
- All trials were funded by the pharmaceutical industry.

A recent analysis of European pharmacovigilance data of individual reports of adverse events occurring while on combined contraceptives found a lower reporting of venous thromboembolism events with combined contraceptives, including natural oestrogens, compared to ethinylestradiol-containing pills. (7) The reported rate of thrombotic events to all reported adverse events for combined E4 and drospirenone pill was 0.07 (34/507), compared to 0.76 (30,022/39,578) for synthetic oestrogen and drospirenone, or 0.28 (3,869/13,583) for synthetic oestrogen and levonorgestrel combination. The findings of this study have a hypothesis-generating nature and cannot be extrapolated to drive a definitive conclusion regarding the safety of investigated formulations.

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