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WALKER, Susan, CLAYDON-MUELLER, Leica, KABIR, Russell, PIERCY, Hilary <http://orcid.org/0000-0002-7663-8858>, MASSEY, Marie-Therese and COSTANZO, Italo

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REVIEW

REPRODUCTIVE, FEMALE AND CHILD HEALTH

Systematic review of factors predictive of unfavourable vaginal bleeding in women of reproductive age using the contraceptive etonogestrel implant

Susan Walker[1] | Leica Claydon-Mueller[1] | Russell Kabir[1] | Hilary Piercy[2] | Marie-Therese Massey[3] | Italo Costanzo[4]

[1]School of Nursing and Midwifery, Faculty of Health, Education, Medicine & Social Care, Anglia Ruskin University, Chelmsford Essex, UK

[2]Department of Nursing and Midwifery, College of Health, Wellbeing and Life Science, Sheffield Hallam University, Sheffield, UK

[3]Wider Workforce, Health Education England, Sheffield, South Yorkshire, UK

[4]Cambridgeshire Community Services NHS Trust, Cambridgeshire, UK

Correspondence

Susan Walker, Faculty of Health, Education, Medicine & Social Care, Anglia Ruskin University, Bishop Hall Ln, Chelmsford Essex CM1 1SQ, UK.
Email: susan.walker@aru.ac.uk

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Abstract

Introduction: This systematic review sought predictors of unfavourable bleeding profiles in women using the etonogestrel contraceptive implant. Unfavourable bleeding is common and a leading cause of requests for removal.

Methods: We included randomised controlled trials (RCTs), and prospective and retrospective cohort studies from 1998 to October 2022. Inclusion criteria were healthy women using etonogestrel for contraception. Papers not in English were excluded as were ongoing or incomplete studies. We searched Pubmed, Pubmed Central, MEDLINE (Web of Science & Ovid), Cochrane library, CINAHL Plus, WHO (HINARI), Open Grey and Greynet.org. Risk of Bias was assessed using ROB2 IRPGv9 for RCTs and ROBINS-I for non-RCTs. We conducted a narrative analysis.

Results: We included 13 studies. Lower body mass index (BMI), younger age, parity and smoking status were statistically, significantly associated with unfavourable bleeding patterns in one or more studies. No studies reported post-partum status having a significant association with unfavourable bleeding. The available data was too limited and too heterogeneous to perform a robust meta-analysis.

Discussion: Heterogeneity in reported outcomes and timescales limited the accuracy of synthesis. Risk of bias was moderate to serious in non-RCTs due to baseline differences and missing or imputed data. The protective effect of higher BMI for unfavourable bleeding is in keeping with previous reviews and studies and is a clinically important finding.

KEYWORDS

contraceptive implant, etonogestrel, predictors, side effects, systematic review, vaginal bleeding

INTRODUCTION

Etonogestrel-containing sub-dermal contraceptive implants are a highly effective, safe, reversible contraception, with few contraindications.[1,2] The method has a duration of 3 years, but has international removal rates of 10%–20%, often due to the side effect of troublesome vaginal bleeding.[1–5] Based on established World Health Organization (WHO) definitions (see Box 1) Mansour et al.[6] dichotomised bleeding patterns on the etonogestrel implant into 'favourable' (amenorrhoea, infrequent bleeding and normal frequency without prolonged bleeding) and 'unfavourable' (prolonged and/or frequent bleeding), and showed that women with unfavourable bleeding patterns were more likely to discontinue the method.[6,7]

This review sought predictors of unfavourable bleeding to help healthcare providers (HCP) advise women, who are considering the etonogestrel implant, on what their bleeding pattern might be.

METHODS

This review is registered with Prospero CRD Register on 27-04-21 Reg No. CRD42021240859.

BOX 1. WHO definitions of bleeding patterns on hormonal contraception

Reference period	Four 90-day periods based on the day of initiating the use of the method: 0–90, 91–180, 181–270 and 271–360
Bleeding or spotting day	Any single day when bloody vaginal discharge was recorded on the menstrual diary
Amenorrhoea	No bleeding or spotting in the reference period
Normal pattern	Neither amenorrhoea, infrequent bleeding, frequent bleeding or irregular bleeding; 3–5 bleeding/spotting days in a 90-day reference period
Frequent bleeding	»5 bleeding/spotting episodes in a 90-day reference period
Prolonged bleeding	Any continuous bleeding/spotting episode lasting more than 14 days in a 90-day reference period. This may overlap with any of the other bleeding patterns except amenorrhoea
Infrequent bleeding	1–2 bleeding/spotting episodes in a 90-day reference period

Research Question: What are the *predictors* of *unfavourable vaginal bleeding* patterns (defined as 'frequent' or 'prolonged' bleeding or 'bleeding leading to a request for removal before 3 years), in *women of reproductive age* who are fitted with the *etonogestrel* contraceptive implant?

Eligibility criteria

The research question was formulated using the PECOS framework.

P. Women of reproductive age—menarche onwards.

I/E. Using the etonogestrel contraceptive implant.

O. Unfavourable × bleeding = defined as frequent or prolonged bleeding or bleeding leading to a request for removal before 3 years.

S. Global. Contraceptive services in both community and acute care facilities (i.e., family doctor, community clinic, maternity setting, acute care setting) or clinical trial setting (Table 1).

Types of participants

All women using etonogestrel-containing contraceptive implants for contraception, regardless of age or country of origin.

Types of interventions

Insertion of etonogestrel-containing contraceptive implant, including post-partum.

Primary outcome measures

Rates of unfavourable (frequent or prolonged) vaginal bleeding rates as side effect, or rates of removal due to vaginal bleeding as a side effect, following insertion of

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Studies: Only original studies/grey literature	
2. Population: Research focusing on women of reproductive age	Non-contraceptive use of implant
3. Design: Randomised controlled trials, observational prospective cohort studies and retrospective cohort studies including secondary analysis	Editorials, reviews, perspectives, case studies
4. Outcomes: unfavourable vaginal bleeding	Other outcomes and side effects
5. Only English language studies	Studies not in English
6. Studies published between 1998 and June 2021	
7. Etonogestrel implant	Levonorgestrel-containing contraceptive implants, e.g., norplant, Jadelle
8. Containing data on associations between bleeding and potential predictors of bleeding	

etonogestrel-containing implant either as descriptive percentages (%) or odds ratio (OR) or relative risk (RR).

Types of studies

We included randomised controlled trials, prospective and retrospective cohort studies.

Language

Studies not written in English were excluded, but studies with an abstract in English were considered for inclusion.

Date range

The date range January 1998 to June 2021 was chosen because the etonogestrel implant became available in the United Kingdom and the United States in 1998.

Studies were grouped by predictor and outcome for synthesis.

Search strategy

Electronic searches

We searched the following electronic databases in April to June 2021, and selected searches were repeated in October 22.

For published articles:

1. Pubmed (last searched 6 October 2022)
2. Pubmed Central (last searched 13 May 2021)
3. MEDLINE (Web of Science & Ovid) (last searched 6 October 2022)
4. Cochrane library
5. CINAHL Plus (last searched 6 October 2022)
6. WHO (HINARI)

For grey literature:

1. Open Grey
2. Greynet.org

We did not look for ongoing or incomplete trials.

Searching other sources

We hand-searched the reference section of included studies and published systematic reviews.

We have provided the search strategies in Supporting Information Files.

Selection process

Two reviewers screened (S. W., H. P.) and a 20% sample of each was checked by two additional reviewers (M. T. M., I. C.) at each round.

The final screening at full-text stage was undertaken by two reviewers (H. P., S. W.), a short reason for exclusion was recorded, and the final selection reviewed and discussed between HP and SW until an agreement was reached.

Screening was not blinded to authors of the paper.

Data collection process

S. W. extracted the data, which was reviewed and checked by R. K.

Data items

Data were extracted for study design, number of participants, predictors, timing of outcome measurement, outcomes, and authors conclusions.

Study risk of bias assessment

Risk of bias was assessed using ROB2 IRPGv9 for RCTs and ROBINS-I for non-RCTs. Two reviewers assessed risk of bias independently, with discussions to resolve differences.

Data extraction

Data were categorised by outcome and predictors.

Outcomes

Outcomes were reports of bleeding complaints, bleeding patterns or removal due to troublesome bleeding.

Bleeding patterns were reported in a heterogeneous manner. To aid comparison, in Table 4, bleeding pattern outcomes were dichotomised into 'unfavourable' bleeding, that is, 'Abnormal bleeding = not amenorrhoeic or infrequent,' and 'favourable' bleeding = normal bleeding, infrequent bleeding or amenorrhoea were possible. Where this was done, the original data is presented in normal font, and the transformed data is presented in italics.

Implant removal for bleeding was compared with no implant removal or with removal for another reason

Definitions of predictors of bleeding

Body mass index (BMI) and age, where defined in the original papers, refer to BMI and age at insertion, except for

Lazorwitz et al.,[8] which is a cross-sectional study recording BMI and bleeding patterns concurrently.

Post-partum insertion was defined as the insertion of the implant up to 8 weeks after birth.

Immediate post-partum insertion was reported as insertion within 48, 96 h or before discharge from a hospital setting after delivery.

Parity was reported in varying categories by different studies, some of which also reported gravidity.

RESULTS

Study selection

Two thousand two hundred fifty citations were retrieved of which 193 were duplicates and removed, leaving 2057 titles. One thousand, three hundred ninety-five titles were ineligible, leaving 662 abstracts to screen. Four hundred eighty abstracts were ineligible leaving 182 full-text papers to screen. One hundred sixty-nine full-text papers were ineligible, because they were duplicate papers or included no predictors of bleeding or no outcome data (Figure 1 PRISMA Diagram). Thirteen papers were included in the systematic review. One important paper,[3] which included the results of eleven open labelled comparative and non-comparative international studies conducted by Organon, was excluded because it was not possible to gain access to the original studies, after contact with the original author and with Organon.[3]

Results of search (Prisma diagram)

Study characteristics

Two studies were non-blinded randomised controlled trails[9,10]; three were prospective cohort studies,[11–13] one was a cross-sectional study comparing bleeding patterns and potential predictors at a single point in time,[8] seven were retrospective cohort studies (Table 2).[14–20] Predictors identified by the included studies were timing of post-partum insertion, age, Body Mass Index (BMI), tobacco use and parity or gravidity. Some studies included 'race'/ethnicity, as a predictor but these demographic concepts are difficult to standardise or accurately assess and so were not included in our review. A few studies recorded prior contraception use, but not in a consistent or standardised manner that allowed inclusion as a predictor.

Heterogeneity in outcomes and predictors

There was a great deal of heterogeneity in the definitions of the study outcomes, and approximations to 'unfavourable bleeding', such as 'heavy bleeding' or 'bleeding complaints' were sometimes reported.

Predictors of bleeding were often secondary outcomes, or had to be extrapolated from predictors of discontinuation, where bleeding was reported as a reason for discontinuation.

There was heterogeneity in the timeframes for the outcomes, which were variously reported at 3, 6, 12 or <36 months (see Table 3).

Additional data was sought from Lazorwitz et al.,[8] Casey et al.,[11] Bryant et al.,[9] and Di Carlo.[12] Only Lazorwitz et al.[8] supplied additional data, which was processed by the reviewers to produce an outcome of "abnormal bleeding—not fewer than 15 bleeding days in 90 days" (i.e., not infrequent or amenorrhoeic).

Reporting bias assessment

Of the two RCTs one[9] scored 'high' overall RoB and one[10] scored low overall RoB. For the non RCTs seven scored 'serious' overall RoB,[14–20] three scored 'moderate'[8,11,13] and one scored 'low' RoB[12] (see Table 3).

Results of individual studies

BMI

BMI as a predictor was explored by six studies.[8,11,12,17,18,20]

Green et al.,[20] Casey et al.,[11] and Di Carlo et al.[12] report that women with lower BMIs are significantly more likely to have unfavourable bleeding or removal due to bleeding.

Casey et al.[11] performed a prospective observational cohort study of 304 women who had implant placements, primarily designed to look at the predictive effect of BMI, with removal indications including removal for bleeding complaints, as a primary outcome. Women with a BMI > 30 kg/m^2 were less likely (OR 2.6 CI [1.2, 5.7] less likely) to have a removal of the implant due to bleeding compared to women with a BMI > 30 kg/m^2, after adjusting for age and parity, and the median BMI for women who had removal for bleeding was statistically significantly lower than the median BMI for women who did not contact a healthcare practitioner (24.6 vs. 27.0 kg/m^2, $p = 0.003$).[11]

Di Carlo et al.[12] in a prospective observational study of 92 women attending a clinic, in a study primarily designed to look at BMI as a predictor of menstrual irregularity, report menstrual bleeding patterns at 3-, 6-, 9-, and 12-month intervals. The study used the WHO definitions of bleeding/spotting and 90-day references periods.[7]

The report divides women into those experiencing 'favourable' bleeding patterns (amenorrhoea, infrequent or normal) for more than 50% of the 90-day references periods up to 12 months ($N = 68$) and those experiencing 'unfavourable' bleeding (frequent or prolonged) in more than 50% of the same reference periods ($N = 18$). Baseline BMI in a group of women with favourable bleeding in >50% of 90-day reference periods (24.84 kg/m^2) is higher than in the

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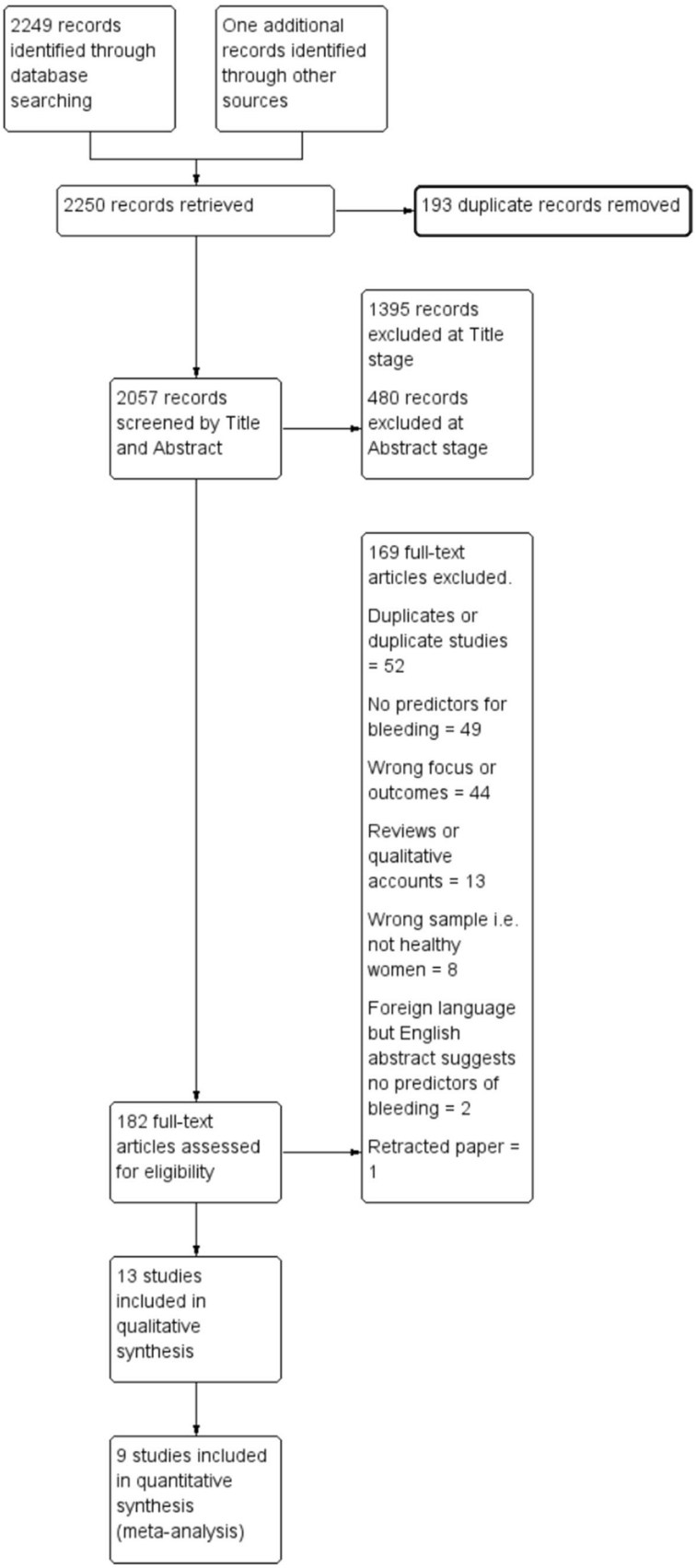

FIGURE 1 Prisma diagram.

TABLE 2 Characteristics of included studies.

References	Study type and design	Participants (*N*)	Predictors	Follow-up (months)	How is bleeding recorded?	Authors conclusions
Bryant et al.[9]	Non-blinded RCT	96 with 64 at end of trial period	Immediate versus 6-week post-partum placement	3, 6, 9, 12	In person or telephone—reported bleeding patterns	None regarding bleeding
Casey et al.[17]	Retrospective review of medical records	115	Age, BMI, parity, post-partum *(race/ethnicity)*	Up to 27 Mean = 7.8	Healthcare practitioner contact for bleeding complaints and removal for bleeding complaints, recorded in notes	No predictors identified
Casey et al.[11]	Observational, prospective cohort including review of notes	304	Looked at age, BMI, parity, post-partum *(race/ethnicity)*	12	Healthcare practitioner contact for bleeding complaints and removal for bleeding complaints, recorded in notes	After adjusting for age and parity, obese women 2.6 times less likely to have implant removal for bleeding
Crockett et al.[19]	Retrospective cohort study derived from review of notes	776 at 6 months, 518 at 12 months	Post-partum placement—immediate, delayed, interval	12	Removal with reason recorded in notes. If no record of removal, continuation assumed	Primary outcome was all removal. After controlling for age, parity, race and BMI, women with post-partum inpatient insertions were less likely to have the implant removed within 12 months (OR = 0.44, 95% CI 0.20–0.97).
Di Carlo et al.[12]	Prospective observational cohort study	99	BMI, weight, height, parity, post-partum *(age at menarche, usual length of menstrual bleed, last contraceptive method)*	12	WHO categories, bleeding diaries	Lower basal BMI may account for higher percentage of irregular bleeding.
Green et al.[20]	Retrospective cohort study derived from review of notes	1200	BMI, age, parity, gravidity, weight	12	'Bothersome' bleeding requiring a follow-up appointment	Younger age and lower BMI were associated with reporting bothersome vaginal bleeding. Patients who were nulliparous or had bothersome bleeding were more likely to have the implant removed in the first year
Ireland et al.[15]	Retrospective cohort study derived from review of notes	414. 259 in immediate post-partum, 49 in delayed post-partum (6-12 weeks), 106 in interval group.	Post-partum versus delayed	36	Removal due to bleeding from medical notes	Immediate post-partum insertion does not lead to increased removal rates compared to delayed or interval insertion
Lazorwitz et al.[8]	Cross-sectional study	350	Age, BMI, *(race/ethnicity, etonogestrel blood levels)*	N/A cross-sectional	Abnormal bleeding (yes/no)—self-report	Increasing serum ENG levels were significantly associated with increasing odds of reporting abnormal bleeding (aOR 1.0008, $p = 0.002$)

TABLE 2 (Continued)

References	Study type and design	Participants (*N*)	Predictors	Follow-up (months)	How is bleeding recorded?	Authors conclusions
Obijuru et al.[18]	Retrospective cohort study derived from review of notes	116	BMI, *(contraceptive method at time of insertion)*	32 (for majority) all at 18 months	Record review- reported side effects	No significant association between BMI, nuisance bleeding and early removal
Peterson et al.[14]	Retrospective cohort study	544	Age, BMI, tobacco use, parity/ gravidity, post-partum *(race/ ethnicity, prior contraception use)*	36	Yes/no documented report of bleeding	In multivariate analysis, two or more pregnancies decreased the odds of bleeding complaints (OR 0.54) and tobacco use increased odd of bleeding complaints (OR: 1.65)
Rai et al.[16]	Retrospective cohort study derived from review of notes	132	Age, parity	Up to 35	Looked at age, parity as predictors of removal due to bleeding but not bleeding per se	Neither age nor parity associated with removal due to bleeding complaints
Vieira et al.[10]	Secondary analysis of open randomised controlled trail	100	Timing of post-partum insertion (<48 hours vs. > 6 weeks)	12	In person visits every 90 days, bleeding diaries. WHO reference used Lochia excluded up to 8 weeks or after 2-day cessation	Immediate versus delayed post-partum insertion have similar bleeding rates at 12 months. Amenorrhoea rates high in both groups
Wahab et al.[13]	Prospective cohort study. Not clear if randomisation occurred	60 post-partum/50 non-post-partum	Post-partum v non-post-partum	6	WHO categories used, not clear but seems to have collected at follow-up visits	No difference in bleeding rates at 3 months but amenorrhoea more common in post-partum grouped at 6 months, and infrequent bleeding more common in non-post-partum

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; ENG, etonogestrel; RCT, randomised controlled trial; WHO, World Health Organization.

TABLE 3 Risk of bias tables.

Robins 1 non RCTs	Bias due to confounding	Bias due to the selection of participants	Bias due to the classification of interventions	Bias due to deviation from the intended intervention	Bias due to missing data	Bias due to measurement of outcomes	Bias due to selective reporting of results	Overall
Casey et al.[17]	Serious	Moderate	Low	Unclear	Serious-missing data, data extraction by one reviewer only	Low (removed for bleeding or not)	Low	Serious
Casey et al.[11]	Moderate	Moderate	Low	Unclear	Low	Moderate	Low	Moderate
Crockett et al.[19]	Serious—statistically significant differences between inpatient and outpatient groups	Moderate	Low	Unclear	Low	Moderate	Low	Serious
Di Carlo et al.[12]	Low	Low	Low	Low	Low	Low	Low	Low
Green et al.[20]	Serious	Moderate	Moderate	N/A	Serious—missing and imputed data	Moderate	Moderate	Serious
Ireland et al.[15]	Serious (differences between groups shown statistically at baseline)	Serious retrospective, loss to follow-up	Low—definition of immediate, delayed and interval is clear	No information	Serious	Low (removed for bleeding or not)	Low—one main outcome (removal)	Serious
Lazorwitz et al.[8]	No information	Low	Low	Moderate to serious—medical records were not available for 100 women	Low—cross-sectional study	Serious—abnormal bleeding is a non-specific category including infrequent and no bleeding. In some case, bleeding categories are not mutually exclusive	Low	Moderate
Obijuru et al.[18]	Unclear	Moderate	Low	Unclear	Serious—only 94/116 had follow-up data	Serious—'nuisance bleeding' not clearly broken down into predictors. Obese/overweight/normal had to be derived from text	Low	Serious
Peterson et al.[14]	Low	Moderate	Low	Not reported	Moderate—missing data ≤ 65 participants	Serious—assumed continuing with implant unless recorded (noted in limitations of paper)	Low	Serious

TABLE 3 (Continued)

Robins 1 non RCTs	Bias due to confounding	Bias due to the selection of participants	Bias due to the classification of interventions	Bias due to deviation from the intended intervention	Bias due to missing data	Bias due to measurement of outcomes	Bias due to selective reporting of results	Overall
Rai et al.[16]	Unclear	Moderate	Low	Unclear	Serious—20/147 lost to follow-up at six weeks and 30/147 lost to follow-up overall	Serious—no direct measurement of 'unfavourable bleeding'. Removal due to bleeding due to heavy/light bleeding recorded. Assumed lifetime use imputed if no data on retention	Low	Serious
Wahab et al.[13]	Serious (no baseline demographic data and no corrections)	Low	Low—post-partum group is clear	Unclear—no Information	Low	Low	Low—all outcomes are reported	Moderate

RCTs	Bias due to randomisation process	Bias due to deviation from intended intervention	Bias due to missing outcome data	Bias due to measurement of outcomes	Overall
Bryant et al.[9]	Low	Unclear	High	Unclear	High
Vieira et al.[10]	Low	Low	Low	Unclear	Low

Abbreviation: RCT, randomised controlled trial.

TABLE 4 Data extraction table.

References	Predictor	Outcomes					
Casey et al.[17]	BMI		No HCP contact for bleeding	HCP contact for bleeding but not removed	Removed for bleeding		
		N	113	19	23		
		BMI	29.1	28	25.8		
		SD	7	6.9	7.2		
Casey et al.[11]	BMI		No HCP contact for bleeding	HCP contact for bleeding but not removed	Removed for bleeding	Removal for bleeding	(aOR) adjusted for age and parity
		N	211	43	50	BMI < 30	1.00
		Mean BMI	28.7	28.4	26	BMI > 30	2.6 (1.2,5.7) less likely
		SD	6.5	9	6.5		
		BMI					
		Normal (<25)	72	21	27		
		Overweight (26–30)	60	7	13		
		Obese (>30)	78	14	10		
		Totals	210	42	50		
Di Carlo et al.[12]	BMI		Favourable bleeding > 50% of RPs 6–12 months	Unfavourable bleeding > 50% RP 6–12 months			
		N	68	18			
		Mean BMI	24.84	20.75			
		SD	4.95	4.41			
Green et al.[20]	BMI		Bleeding appointment ($n = 268$)	No bleeding appointment ($n = 932$)			
		Median BMI	23.5	24.2			

TABLE 4 (Continued)

References	Predictor	Outcomes				
Lazorwitz et al.[8]	BMI		Abnormal bleeding at > 12 months post-insertion: Y		Favourable at 12 months (calculated from data supplied by author)	Unfavourable at 12 months (calculated from data supplied by author)
		N	208/350	*N*	196	154
		BMI	OR 0.98 (0.94, 1.01)	BMI	27.96	25.78
				SD	6.37	4.98
Obijuru et al.[18]	BMI	Irregular bleeding at 36 months				
		Obese (BMI > 30)	'32% of 22'	7.04		
		Overweight (BMI 25–29.9)	'47% of 17'	7.99		
		Normal weight (BMI < 25)	'34% of 67'	22.78		
		Totals	106			
Casey et al.[17]	Age		No HCP contact for bleeding	HCP contact for bleeding but not removed	Removed for bleeding	
		N	113	19	23	
		Mean age	25.8	24.4	24.6	
		SD	7.6	5.9	4.5	
Casey et al.[11]	Age		No HCP contact for bleeding	HCP contact for bleeding but not removed	Removed for bleeding	
		N	211	43	50	
		Mean age	24.2	23.4	24.4	
		SD	6.6	6.3	6.1	
Di Carlo et al.[12]	Age		Favourable bleeding >50% RPs 6–12 months	Unfavourable bleeding >50% RP 6–12 months)		
		Mean age	32.3	30.1		
		SD	7.4	6.6		

(Continues)

TABLE 4 (Continued)

References	Predictor	Outcomes				
Green et al.[20]	Age		Bleeding appointment ($n = 268$)	No bleeding appointment ($n = 932$)		
		Median age	18.9	19.4		
Lazorwitz et al.[8]	Age		Abnormal bleeding at > 12 months post-insertion: Y		Favourable at 12 months (calculated from data supplied by author)	Unfavourable at 12 months (calculated from data supplied by author)
		N	208 (of 350)	*N*	196	154
		Age (OR)	0.97 (0.91, 1.03)	Mean age	23.2549	22.99
				SD	3.52	3.196
Rai et al.[16]	Age		Removal for bleeding within confirmed lifetime of device	Removal for bleeding within assumed lifetime of device		
		Cox's hazard ratios	0.94	0.92		
		p value	0.22	0.11		
Casey et al.[17]	Post-partum v non-post-partum		No HCP contact for bleeding	HCP contact for bleeding but not removed	Removed for bleeding	Totals
		N	113	19	23	
		Post-partum placement	30	8	9	47
		Non-post-partum placement	83	11	14	108
		Breastfeeding	21	5	3	29
Casey et al.[11]	Post-partum v non-post-partum		No HCP contact for bleeding	HCP contact for bleeding but not removed	Removed for bleeding	Totals
		N	211	43	50	304
		Post-partum	55	10	16	81
		Non-post-partum	156	33	34	223
		Lactating at placement	30	2	10	42

TABLE 4 (Continued)

References	Predictor	Outcomes						
		Not lactating at placement	167	39	39	245		
		Lactation status unknown	14	2	1	17		
Crockett et al.[19]	Post-partum v non-post-partum		Removal due to bleeding by 12 months	Removal due to bleeding by 6 months				
		Interval	16/275	6/319				
		Post-partum (immed + delayed < 8 weeks)	16/243	12/457				
		Totals *N*	32/518	18/776				
Ireland et al.[15]	Post-partum v non-post-partum		Implant removed for bleeding < 36 months (yes)	Implant removed for bleeding < 36 months (no)				
		Immediate post-partum (*n*)	50	209				
		Delayed post-partum (*n*)	9	40				
		Interval (*N*)	22	84				
		Totals	81	313	Total = 414			
Wahab et al.[13]	Post-partum versus non-post-partum	Bleeding pattern at 6 months follow-up duration						
			Amenorrhoea	Infrequent	Normal	Favourable, that is, amenorrhoea, infrequent, normal	Frequent	Prolonged	Unfavourable, that is, frequent, prolonged
		Post-partum (*N*)	39	5	7	51	6	3	9
		Non-post-partum (*N*)	19	12	8	39	8	3	11
Bryant et al.[9]	Immediate post-partum versus delayed post-partum		Heavier, prolonged bleeding or cramps at 12 months	Removed due to bleeding before 12 months	Totals				
		Immediate post-partum insertion (*n* = 37)	25	3	28/37				

(Continues)

TABLE 4 (Continued)

References	Predictor	Outcomes							
		Delayed post-partum insertion at 6 weeks ($n = 27$)	18	0	18/27				
Crockett et al.[19]	Immediate versus delayed post-partum		Removal due to bleeding by 6 months $N = 457$		Removal due to bleeding by 12 months $N = 243$				
		Immediate post-partum (inpatient): $n = 342$	9	Immediate post-partum (inpatient): $n = 139$	7				
		Delayed post-partum < 8 weeks: $n = 115$	3	Delayed post-partum < 8 weeks: $n = 104$	9				
		Totals	12/457		16/243				
Ireland et al.[15]	Immediate post-partum versu delayed post-partum		Implant removed for bleeding before 36 moths: yes	Implant removed for bleeding before 36 moths: no	Totals				
		Immediate post-partum (<96 h)	50	209	259				
		Delayed post-partum (6–12 weeks)	9	40	49				
		Interval	22	84	106				
					414				
Vieira et al.[10]	Immediate versus delayed post-partum		Bleeding pattern at RP4: 12 months						
			Amenorrhoea	Infrequent	Normal	Favourable, that is, amenorrhoea, Infrequent, Normal	Frequent	Prolonged	Unfavourable, that is, frequent, prolonged	Missing
		Early post-partum (48 h)	26	11	3	40	4	1	5	6
		Delayed Post-partum (6 weeks)	23	7	6	36	5	1	6	9

TABLE 4 (Continued)

References	Predictor	Outcomes							
			Bleeding pattern at RP2: 6 months						
			Amenorrhoea	Infrequent	Normal	Favourable, that is, amenorrhoea, Infrequent, Normal	Frequent	Prolonged	Unfavourable, that is, frequent, prolonged	Missing
		Early post-partum (48 h)	26	7	2	35	7	1	8	8
		Delayed Post-partum (6 weeks)	28	11	2	41	3	1	4	6
Casey et al.[17]	Parity/gravidity		No HCP contact for bleeding	HCP contact for bleeding but not removed	No removal	Removed for bleeding	Totals			
		Parity < 3	95	16	111	21	132			
		Parity ≥ 3	18	3	21	2	23			
		Total	113	19	132	23	156			
Casey et al.[11]	Parity/gravidity	Parity	No HCP contact for bleeding	HCP contact for bleeding but not removed	No removal	Removed for bleeding	Totals			
		0	117	23	140	25	165			
		1 or 2	67	15	82	19	101			
		<3	184	38	222	44	266			
		≥3	27	5	33	6	38			
		Totals (bleeding)	211	43	254	50	304			
Di Carlo et al.[12]	Parity/gravidity		Favourable > 50% RP 6–12 months	Unfavourable > 50% RP - 6–12 months	Total (parity) = 86					
		Parity								
		≤1	12	1	13					
		2–3	38	4	42					
		≥4	18	13	31					
		Totals (bleeding)	68	18	86					
Green et al.[20]	Parity/gravidity		Bleeding appointment (n = 268)	No bleeding appointment (n = 932)						
		Nulligravid	74.30%	72.40%						
		Nulliparous	77.20%	77.90%						

(Continues)

TABLE 4 (Continued)

References	Predictor	Outcomes				
Peterson et al.[14]	Parity/Gravidity			Bleeding complaint Y/N within 12 months: OR	$N = 544$	
		Gravid 0 $n = 83$	1		83	
		Gravid 1 $n = 188$	0.65 (0.38, 1.13)		188	
		Gravid > 2 $n = 266$	0.54 (0.32, 0.91)		266	
					7 missing data	
Rai et al.[16]	Parity/gravidity			Removal for bleeding within confirmed lifetime of device		Removal for bleeding within assumed lifetime of device
		Cox's hazard ratios	1.14			1.05
		p values	0.9			0.77

Abbreviations: BMI, body mass index; HCP, healthcare provider; SD, standard deviation.

group of women with unfavourable bleeding (20.75 kg/m^2) ($p < 0.005$).[12]

Green et al.,[20] who reviewed the charts of 1200 adolescents aged 12–24 years to determine demographic factors associated with 'bothersome bleeding' (defined as bleeding resulting in or addressed in a consultation) reported a statistically significant difference in median BMIs, with a median BMI of 23.5 kg/m^2 in adolescent women who had made an appointment for bleeding in the 12 months post-insertion compared to a median BMI of 24.2 kg/m^2 for those who had not ($p = 0.04$). There was no statistically significant difference detected in absolute weight (kg) between women with appointments for bleeding and those without.

Lazorwitz et al.,[8] Obijuru et al.,[18] and Casey et al.[17] report no significant association of BMI with various 'unfavourable' bleeding outcomes.

Casey et al.[17] carried out a retrospective review of 155 medical records with a primary outcome of requests for removal for bleeding changes and report the mean [and standard deviation (SD)] BMI of those with no HCP contact for bleeding (29.1 kg [SD 7.0]), with HCP contact for bleeding but no removal (28.0 kg [SD 6.9]) and with removal for bleeding (25.8 kg [SD 7.2]). The authors state that BMI was not a statistically significant risk for bleeding or implant removal (for any reason).[17]

Obijuru et al.[18] reviewed the charts of 116 adolescents following contraceptive implant insertion, reporting on 94 individuals. She reports removal rates for nuisance bleeding and rates of undefined "irregular bleeding."

In total, 48% (45/94) experienced nuisance bleeding and 18% (17/94) had a removal due to bleeding. No association was found between BMI and nuisance bleeding or early implant removal (defined as <32 months use).[18]

Lazorwitz et al.[8] report on a cross-sectional prospective study whose primary outcome was the effect of etonogestrel (ENG) concentration after 12 months on bleeding. The bleeding profiles were assessed by brief questionnaire, and it was not possible to categorise them by WHO criteria.[8]

BMI was not significantly associated with Abnormal bleeding (yes/no; $N = 208$) OR = 0.98 (95% CI 0.94, 1.01), amenorrhoea (yes/no; $N = 52$), OR = 1.01 (95% CI 0.97, 1.07) or with reporting a current monthly period (yes/no; $N = 132$) OR = 0.98 (95% CI 0.95, 1.02).

Age

Age was explored as a potential predictor by six studies.[8,11,12,16,17,20]

Lazorwitz et al.,[8] Di Carlo et al.,[12] Casey et al.,[11] Casey et al.,[17] and Rai et al.[16] report no association of age with 'unfavourable' bleeding or removal due to bleeding.

Rai et al.[16] in a small retrospective study of 147 women fitted with an implant in a general practice setting, calculated the Cox's hazard ratio for bleeding at different

ages and found no significant association using confirmed (hazard ratio (confirmed lifetime of device) = 0.94, $p = 0.22$).

Casey et al.[11] in a prospective observational study of 304 women (see above) found no significant differences ($p = 0.7$) in mean age between those with no HCP contact for bleeding (mean = 24.2 years, SD = 6.6), those with an HCP contact for bleeding but no removal (mean = 23.4 years, SD = 6.3) and those with a removal due to bleeding (mean = 24.4 years, SD = 6.1).

Lazorwitz et al.[8] in a prospective, cross-sectional study primarily looking at etonogestrel concentrations in 350 women (see above) provided univariate ORs for age and abnormal bleeding (OR = 0.97; 95% CI 0.91, 1.03), amenorrhoea (OR = 1.0; 95% CI 0.91, 1.09) and a reported current monthly bleed (OR = 1.02; 95% CI 0.95, 1.08).

Di Carlo et al.[12] in a prospective, observational study of 86 women (see above) reported no difference in mean ages between those who had a 'favourable' bleeding pattern (mean age = 32.3 years [SD 7.4]) and those who had an 'unfavourable' bleeding pattern (mean age = 30.1 years; SD 6.6), $p = 0.27$.

Casey et al.[17] reports mean age for those with no HCP contact for bleeding (25.8 years [SD 7.6]), with HCP contact for bleeding but no removal (24.4 years [SD 5.9]) and with removal due to bleeding (24.6 years [SD 4.5]), and states that age was not a statistically significant risk for reported bleeding or implant removal (for any reason).

Only Green et al.[20] reports a statistically significant median difference in age, with a median of 18.9 years in adolescent women who had made an appointment for bleeding in the 12 months post-insertion compared to a median BMI of 19.4 years for those who had not ($p = 0.01$).

Post-partum insertion

Seven studies looked at post-partum insertion as a predictor, either as a primary or secondary variable.[9–11,13,15,17,19] None found statistically significant differences in unfavourable bleeding patterns between post-partum and non-post-partum insertion.

Wahab et al.[13] in a prospective cohort study, compared bleeding rates 3 and 6 months after insertion between women who had an implant inserted within 8 weeks of delivery ($N = 60$) compared within women who had an insertion in a non-post-partum setting ($N = 50$) at least 6 months after delivery.

Women were followed up at 3 and 6 months and WHO 90-day reference period categorisation of bleeding was used. The study found no statistically significant difference in bleeding rates at 3 months, although there was a trend towards greater amenorrhoea in the post-partum group.[13] The authors excluded nulliparous women from their recruited sample, and do not comment on whether post-partum women were breastfeeding. Since breastfeeding is likely to affect post-partum bleeding patterns, this is a limitation of the study.

Ireland et al.[15] in a retrospective cohort study, compared the discontinuation rate of the implant due to irregular bleeding, in women with immediate post-partum insertion (within 96 h) compared to delayed post-partum insertion (6–12 weeks) and non-post-partum placement (more than 12 weeks after delivery). The primary outcome was '% removed due to irregular bleeding' in each of the three groups.[15] No significant difference was found in percentage removal due to irregular bleeding between immediate (19.3%), delayed (18.4%) and interval (20.8%) insertions.[15] No data was supplied on breastfeeding patterns in post-partum women, which is a limitation of the study.

Vieira et al.[10] performed a secondary analysis of an open randomised-controlled trial of 100 women receiving the ENG contraceptive implant either early post-partum (within 48 h of delivery) or delayed post-partum (at 6 weeks post-partum) and reports similar bleeding rates for both groups at 3, 6, 9 and 12 months. Vieira et al.[10] report that they performed a sub-analysis of amenorrhoea between exclusive and partially breastfeeding women at 3 and 6 months, which were similar in both groups.

Bryant et al.[9] compared immediate (before hospital discharge) post-partum placement with delayed placement at 6 weeks in post-partum adolescents aged 14–24 years in a randomised controlled trial. Follow-up data on bleeding patterns was not the primary outcome of the study but no significant difference was reported in 'Heavy, irregular bleeding or severe cramping' at 12 months.[9] The authors report breastfeeding rates at 3, 6, 9 and 12 months, but because bleeding patterns were not a primary outcome of the study, insufficient data is provided to compare the effect of breastfeeding on bleeding patterns.

After adjusting for age and BMI Casey et al.[11] found no association with post-partum placement and removal for bleeding (OR = 1.5; 95% CI 0.8, 3.0). The authors report no significant association with placement during lactation and removal for bleeding, after adjusting for age and BMI (OR = 0.9; 95% CI 0.8, 1.1).

Crockett et al.[19] conducted a retrospective cohort study for all women receiving the etonogestrel implant immediately post-partum (i.e. before postnatal discharge), delayed post-partum (<8 weeks after birth) or non-post-partum between 1 July 2007, and 30 June 2014. The primary outcome was implant removal but reasons for removal allowed examination of removal due to bleeding. There was no statistically significant difference between the inpatient or outpatient groups for removal due to bleeding at either 6 or 12 months.[19] The study found a lower OR of removal for any reason at 12 months for those women who received the implant as inpatients, compared to both delayed and interval insertion (aOR 0.44 [95% CI 0.22, 0.97]). The authors report that there were no removals due to problems with breastfeeding but do not report if breastfeeding rates differed between the two post-partum groups in this retrospective study.

Casey et al.[17] report that neither post-partum nor breastfeeding status were statistically significant risks for reported bleeding or implant removal (for any reason).

Parity/gravidity as predictor

Six papers looked at parity/gravidity as a predictor.[11,12,16,17,2014] Parity refers to any pregnancy beyond 24 weeks whilst gravidity refers to any pregnancy.

Two[1214] found an effect of gravidity or parity on reported bleeding but in opposite directions. The remaining four report no association.

Peterson et al.[14] in a retrospective cohort study of all 544 women receiving an implant at a US hospital, designed to look at predictors of implant discontinuation within 12 months of insertion, report documented complaints of bleeding (Y/N) within the 12-month period. Using gravidity = 0 as a reference, women with one prior pregnancy had an OR = 0.65, CI (0.38, 1.13) of having documented bleeding complaints, and women with two or more prior pregnancies had an OR = 0.54, CI (0.32, 0.91) of bleeding complaints.

Bivariate analysis showed a significant association between lower gravidity and documented bleeding complaint ($p = 0.02$)

Di Carlo et al.[12] report that, for women with a history of one or no pregnancies, 92% (12/13) had 'favourable' and 8% (1/13) 'unfavourable' bleeding patterns. Of those with a history of 2–3 pregnancies, 90% (38/42) had 'favourable' and 10% (4/42) 'unfavourable' bleeding patterns. Of multiparous women with a history of four or more pregnancies, 58% (18/31) reported 'favourable' and 42% (13/31) reported 'unfavourable' bleeding. These differences are statistically significant ($p = 0.002$).

This finding is opposite to that of Peterson, in that multiparity (i.e., higher gravidity) is associated with unfavourable bleeding.

Casey et al.[11] reports no significant difference between women with parity = 0, parity = 1–2, or parity ≥ 3, in terms of bleeding complaints or removal for bleeding complaints ($p = 0.94$).

Rai et al.[16] in a small retrospective study of 147 women fitted with an implant in a general practice setting, found no significant association between parity and bleeding complaints (Hazard ration [confirmed lifetime of device] = 1.14, $p = 0.47$).

Casey et al.[17] report that parity, defined as, < 3 or >= 3, was not a statistically significant risks for reported bleeding or implant removal (for any reason).

Green et al.[20] report no statistically significant difference in the percentages of women reporting nulliparity or nulligravidity, between the group of adolescent women who made an appointment for bleeding in the 12 months post-insertion and those who did not.

Tobacco use

Peterson et al.[14] in a retrospective chart review reports that bivariate analysis showed a significant association between tobacco use and documented bleeding complaints (yes/no) ($p = 0.006$).

In multi-variate analysis tobacco use had an OR of 1.65 95% (CI 0.99, 2.76) for a recorded complaint of bleeding within 12 months.

DISCUSSION

Overall completeness and applicability of evidence

BMI and age were clearly reported in the papers. Groupings for parity and gravidity were variable, and immediate and delayed post-partum status showed minor variations in definition. Outcomes and timeframes for the outcomes were very varied. In addition, bleeding outcomes were often not the primary outcome for which the data was gathered. Of these, 'removal for bleeding' was the most clearly and consistently reported outcome, but the timeframe varied between 11 and 36 months.

Bleeding patterns were reported according to WHO definitions by Vieira et al.[10] and Wahab et al.,[13] but 'favourable' and 'unfavourable' bleeding patterns had to be calculated, extrapolated, or estimated for Lazorwitz et al.,[8] Casey et al.,[11,17] Bryant et al.[9] and Obijuru et al.[18] The period in which bleeding complaints were reported varied between 6 months after insertion to 36 months. Di Carlo et al.[12] used WHO reported measure of bleeding but amalgamated the data to produce two groups of women with 'favourable' or 'unfavourable' bleeding' in more than 50% of 'reference periods'.

The evidence for predictors of bleeding patterns is strongest for BMI, age and post-partum status.

Women with lower BMIs have more unfavourable bleeding and a greater chance of removal for bleeding in three of the six studies who included it. The other three studies did not demonstrate any effect of BMI.

Of the six studies which recorded age as a potential predictor, only Green et al.[20] found a statistically significant effect, reporting that younger age was associated with greater chance of making an appointment because of bleeding complaints. All of Green's participants were adolescents under the age of 25 years.

None of the seven studies which assessed or reported the effect of post-partum status showed an effect on bleeding pattern.[9-11,13,15,17,19] Breastfeeding is likely to influence bleeding patterns since exclusive breastfeeding can inhibit ovulation, but it was reported in only two of the seven papers which included post-partum women.[11,17] In one of these,[11] a retrospective study, breastfeeding at the time of insertion is recorded but not at the time of reported bleeding complaints. In an earlier study by the same authors[17] breastfeeding is recorded but no indication is given about whether breastfeeding was at the time of insertion or at the time of reported bleeding complaints. This means that little can be concluded regarding the effect of breastfeeding on unfavourable bleeding patterns from these studies. The effect of concurrent

breastfeeding on bleeding patterns in women who choose an etonogestrel implant in the post-partum period is an area for future research.

Quality of evidence

Given the above limitations, the quality of the evidence is moderate to low in this systematic review.

The risk of bias in the RCTs is low in Vieira et al.[10] but high in Bryant et al.,[9] due to missing data, and uncertainty in terms of measurement of the outcome, because bleeding patterns were a secondary outcome.

In the non-RCTs, the risk of bias is moderate to serious in all but Di Carlo,[12] due to the retrospective nature of the studies,[16–20] differences between groups at baseline,[15,19,20] missing data,[14–18,20] or inexact measurement and/or reporting of the outcomes of interest.[8,14,16,18,20]

Limitations of the review

For outcomes, we chose to use 'favourable' and 'unfavourable' bleeding definitions, which we defined at the outset of the review, based on Mansour et al.[6] 'Favourable bleeding' included normal, infrequent or no bleeding, and 'unfavourable bleeding' included frequent or prolonged bleeding or a request for removal due to bleeding. However, due to the variety of descriptions used to report bleeding outcomes, we were unable to adhere strictly to these definitions, and sometimes had to extrapolate from what was reported, for example, 'Healthcare Provider Contact for bleeding complaint' was accepted as 'unfavourable bleeding'. The report of bleeding complaints or attendance at a clinic for such complaints is likely to be influenced by the tolerance of women for such bleeding changes, and this is highly likely to be affected by age and other psycho-social characteristics.

The outcome of 'removal for bleeding' was more consistently defined and reported.

Throughout, we have tried to ensure that the outcomes compared were sensible and practical in terms of clinicians advising women of the potential bleeding outcomes.

We were unable to obtain data used in Mansour et al.[3] (see above) and so were unable to include a significant amount of data which would have fitted our inclusion criteria.

Agreements and disagreements with other sources

Our finding that BMI is associated with bleeding outcomes, and that women with higher BMIs are less likely to report unfavourable bleeding, is in keeping with the review performed by Mansour et al.,[3] who report a highly significant negative correlation between BMI and mean number of bleeding days per reference period ($r = -1.772$, $p < 0.0001$). In keeping with our findings, Mansour et al.[3] found no association with age or parity and bleeding days per reference period.

CONCLUSIONS

This systematic review has shown that higher BMI is most often associated with fewer complaints of unfavourable bleeding.

Post-partum status and age appear not to affect bleeding patterns.

More research is required to ascertain whether parity/gravidity, previous contraception, concurrent breastfeeding, or tobacco use has a predictive effect on bleeding patterns when using the etonogestrel implant.

The data from the included studies were too limited to allow robust meta-analysis. Where possible, studies examining side effects of the etonogestrel implant should seek to use standardised bleeding descriptions to allow future meta-analysis to be conducted.

Implications for practice

Women can be reassured that age and post-partum status are unlikely to affect whether they experience an unfavourable bleeding pattern.

Women with higher BMIs can be told that they are less likely to experience unfavourable bleeding.

Implications for research

Prospective research in this area should record not only removals, but reasons for removal, so that removals for bleeding can be identified. When recording bleeding complaints, the WHO definitions of bleeding should be used and reported where possible, with less reliance on proxy measures such as requesting a healthcare contact, and bleeding patterns should be recorded up to 12 months after insertion.

The effect or predictive value of prior contraceptive use on bleeding patterns would be a useful addition to predictive estimates, in particular, the relationship between bleeding patterns with the desogestrel contraceptive pill, which is metabolised to etonogestrel, and subsequent bleeding patterns when using the etonogestrel implant. Careful prospective observational studies or rigorous and comprehensive retrospective longitudinal studies will help to clarify if any predictive association exists.

AUTHOR CONTRIBUTIONS

Susan Walker: conceptualisation (lead), investigation, analysis, methodology, writing – original draft(lead), writing – review and editing. **Hilary Piercy:** investigation, analysis, writing – review and editing. **Leica Claydon-Mueller:** investigation, analysis, methodology (lead), writing – review and

editing. **Russell Kabir**: investigation, analysis, methodology, writing – review and editing (supporting). **Marie-Therese Massey:** Investigation, analysis, writing – review and editing (supporting). **Italo Costanzo:** investigation, analysis, writing – review and editing (supporting).

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CONFLICT OF INTEREST STATEMENT

Susan Walker has previously received funding from Bayer PLC. The remaining authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

This paper did not produce any new data.

ETHICS STATEMENT

No ethical review was necessary for this paper.

ORCID

Susan Walker https://orcid.org/0000-0002-2426-1470
Leica Claydon-Mueller https://orcid.org/0000-0002-0428-3955
Russell Kabir https://orcid.org/0000-0001-9257-2775
Hilary Piercy https://orcid.org/0000-0002-7663-8858
Italo Costanzo https://orcid.org/0000-0002-0493-0462

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