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

## 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 BMI, younger age, parity, and smoking status were statistically, significantly associated with unfavourable bleeding patterns in one or more studies. No studies reported postpartum 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 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.

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## Keywords (up to 7)

Contraceptive implant

Side effects

Vaginal bleeding

Predictors

Systematic Review

Etonogestrel

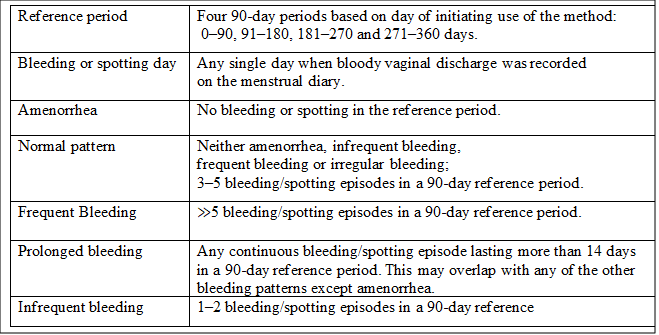
## Practitioner Points (3)

* Women with higher BMIs may be advised that they are less likely to experience unfavourable bleeding patterns after etonogestrel contraceptive implant insertion compared to women with lower BMIs.
* Women may be advised that post-partum insertion of an etonogestrel contraceptive implant is unlikely to increase their risk of unfavourable bleeding compared to interval insertion

## Introduction

Etonogestrel-containing sub-dermal contraceptive implants are a highly effective, safe, reversible contraception, with few contraindications 12. The method has a duration of three years, but has international removal rates of 10-20%, often due to the side effect of troublesome vaginal bleeding 1234 5. Based on established World Health organisation (WHO) definitions (See Box1) Mansour et al. (2019) 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 advise women, who are considering the etonogestrel implant, on what their bleeding pattern might be.

**Box 1. WHO definitions of bleeding patterns on Hormonal Contraception**

## Methods

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

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 **etonorgestrel** contraceptive implant?

### Eligibility criteria

The research question was formulated using the PECOS framework.

P. Women of reproductive age – menarche onwards

I/E. Using the etonorgestrel 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. Inclusion and exclusion criteria**

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| --- | --- |
| **Table 1. Inclusion and Exclusion criteria** | |
| **Inclusion criteria** | Exclusion criteria |
| 1. **Studies: Only original studies/grey literature** |  |
| 1. **Population: Research focusing on women of reproductive age** | Non-contraceptive use of implant |
| 1. **Design: Randomised controlled trials, Observational prospective cohort studies and retrospective cohort studies including secondary analysis** | Editorials, reviews, perspectives, case studies |
| 1. **Outcomes: unfavourable vaginal bleeding** | Other outcomes and side effects |
| 1. **Only English Language studies** | Studies not in English |
| 1. **Studies Published between 1998 to June 2021** |  |
| 1. **Etonogestrel implant** | Levonorgestrel-containing contraceptive implants e.g. Norplant, Jadelle |
| 1. **Containing data on associations between bleeding and potential predictors of bleeding** |  |

### Types of Participants

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

### Types of Interventions

Insertion of etonorgestrel-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 etonorgestrel-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 etonorgestrel implant became available in the UK and US in 1998.

Studies were grouped by predictor and outcome for synthesis.

### Search Strategy

#### **Electronic Searches**

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

For published articles:

1. Pubmed (last searched 06-10-22)

2. Pubmed Central (last searched 13-05-21)

3. MEDLINE (Web of Science & Ovid) (last searched 06-10-22)

4. Cochrane library

5. CINAHL Plus (last searched 06-10-22)

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 Supplementary Files.

### Selection Process

Two reviewers screened (SW, HP) and a 20% sample of each was checked by two additional reviewers (MTM, IC) at each round.

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

Screening was not blinded to authors of the paper.

### Data Collection Process

SW extracted the data, which was reviewed and checked by RK.

### 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 heterogenous manner. To aid comparison, in the Data Extraction table (Table 4), bleeding pattern outcomes were dichotomised into ‘unfavourable’ bleeding i.e. ‘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

BMI and age, where defined in the original papers, refer to BMI and age at insertion, except for Lazorwitz (2019) which is a cross sectional study recording BMI and bleeding patterns concurrently.

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

Immediate post-partum insertion was reported as insertion within 48 hours, 96 hours 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

2250 citations were retrieved of which 193 were duplicates and removed, leaving 2057 titles. 1395 titles were ineligible, leaving 662 abstracts to screen. 480 abstracts were ineligible leaving 182 full text papers to screen. 169 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 (Mansour 2008), 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, despite contact with the original author and with Organon8.

#### Results of Search (Prisma Diagram)

**Figure 1 Prisma Diagram**

### Study Characteristics

Two studies were non-blinded randomised controlled trails (Bryant 2017; Vieira 2019 9 10), three were prospective cohort studies (Casey 2013, Di Carlo 2015, Wahab 2016) 11–13, one was a cross sectional study comparing bleeding patterns and potential predictors at a single point in time (Lazorwitz 2019) 14 , seven were retrospective cohort studies (Petersen 2019, Ireland 2014, Rai 2004, Casey 2011, Obijuru 2016, Crockett 2017, & Green 2021) (Table 2) 15,16 17–21 . Predictors identified by the included studies were timing of post-partum insertion, age, 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.

**Table 2 Characteristics of Included Studies**

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| Table 2 Characteristics of Included Studies | | | | | | |
| Citation | **Study type & design** | **Participants (N)** | **Predictors** | **Follow up (months)** | **How is bleeding recorded?** | **Authors conclusions** |
| Bryant, A. G., Bauer, A. E., Stuart, G. S., Levi, E. E., Zerden, M. L., Danvers, A., & Garrett, J. M. (2017). Etonogestrel-Releasing Contraceptive Implant for Postpartum Adolescents: A Randomized Controlled Trial. *Journal of Pediatric and Adolescent Gynecology*, *30*(3), 389–394. <https://doi.org/10.1016/J.JPAG.2016.08.003> | Non blinded RCT | 96 with 64 at end of trial period | immediate v 6-week postpartum placement | 3,6,9,12 | in person or telephone - reported bleeding patterns | None regarding bleeding |
| Casey, P. M., Long, M. E., Marnach, M. L., & Bury, J. E. (2011). Bleeding related to etonogestrel subdermal implant in a US population. *Contraception*, *83*(5), 426–430. <https://doi.org/10.1016/j.contraception.2010.09.012> | Retrospective review of medical records | 115 | Age, BMI, parity, postpartum *(Race/ethnicity)* | Up to 27 Mean 7.8 | Health Care Practitioner contact for bleeding complaints and removal for bleeding complaints, recorded in notes | No predictors identified |
| Casey, P. M., Long, M. E., Marnach, M. L., Fleming-Harvey, J., Drozdowicz, L. B., & Weaver, A. L. (2013). Association of body mass index with removal of etonogestrel subdermal implant. *Contraception*, *87*(3), 370–374. <https://doi.org/10.1016/j.contraception.2012.08.001> | Observational, prospective cohort including review of notes | 304 | Looked at age, BMI, parity, postpartum *(Race/ethnicity)* | 12 | Health Care 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 ESI removal for bleeding |
| Crockett, A. H., Pickell, L. B., Heberlein, E. C., Billings, D. L., & Mills, B. (2017). Six- and twelve-month documented removal rates among women electing postpartum inpatient compared to delayed or interval contraceptive implant insertions after Medicaid payment reform. Contraception, 95(1), 71–76. <https://doi.org/10.1016/j.contraception.2016.07.004> | 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 body mass index, women with postpartum inpatient insertions were less likely to have the implant removed within 12 months (OR=0.44, 95% CI 0.20–0.97). |
| Di Carlo, C., Guida, M., De Rosa, N., Sansone, A., Gargano, V., Cagnacci, A., & Nappi, C. (2015). Bleeding profile in users of an etonogestrel sub-dermal implant: effects of anthropometric variables. An observational uncontrolled preliminary study in Italian population. *Gynecological Endocrinology : The Official Journal of the International Society of Gynecological Endocrinology*, *31*(6), 491–494. <https://doi.org/https://dx.doi.org/10.3109/09513590.2015.1018163> | Prospective observational cohort study | 99 | BMI, weight, height, parity, postpartum  *(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, S., Sheeder, J., & Richards, M. (2021). The Etonogestrel Implant in Adolescents: Factors Associated With Removal for Bothersome Bleeding in the First Year After Insertion. Journal of Pediatric and Adolescent Gynecology, 34(6), 825–831. <https://doi.org/10.1016/j.jpag.2021.05.011> | 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 body mass index 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, L. D., Goyal, V., Raker, C. A., Murray, A., & Allen, R. H. (2014). The effect of immediate postpartum compared to delayed postpartum and interval etonogestrel contraceptive implant insertion on removal rates for bleeding. *Contraception*, *90*(3), 253–258. <https://doi.org/https://dx.doi.org/10.1016/j.contraception.2014.05.010> | Retrospective cohort study derived from review of notes | 414.  259 in immediate postpartum, 49 in delayed postpartum (6-12 weeks), 106 in interval group. | Postpartum v delayed | 36 | Removal due to bleeding from medical notes. | Immediate postpartum insertion does not lead to increased removal rates compared to delayed or interval insertion |
| Lazorwitz, A., Aquilante, C. L., Dindinger, E., Harrison, M., Sheeder, J., & Teal, S. (2019). Relationship Between Etonogestrel Concentrations and Bleeding Patterns in Contraceptive Implant Users. *Obstetrics and Gynecology*, *134*(4), 807–813. <https://doi.org/10.1097/AOG.0000000000003452> | 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) |
| Obijuru, L., Bumpus, S., Auinger, P., & Baldwin, C. D. (2016). Etonogestrel Implants in Adolescents: Experience, Satisfaction, and Continuation. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*, *58*(3), 284–289. <https://doi.org/10.1016/j.jadohealth.2015.10.254> | 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, A. M., Brown, A., Savage, A., & Dempsey, A. (2019). Prevalence of early discontinuation and associated factors among a retrospective cohort of etonogestrel contraceptive implant users. *The European Journal of Contraception & Reproductive Health Care*, *24*(6), 475–479. <https://doi.org/10.1080/13625187.2019.1666361> | Retrospective cohort study | 544 | Age, BMI, tobacco use, parity/  gravidity, postpartum *(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, K., Gupta, S., & Cotter, S. (2004). Experience with Implanon in a northeast London family planning clinic. *The European Journal of Contraception & Reproductive Health Care : The Official Journal of the European Society of Contraception*, *9*(1), 39–46. <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=15352694> | 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, C. S., de Nadai, M. N., de Melo Pereira do Carmo, L. S., Braga, G. C., Infante, B. F., Stifani, B. M., Ferriani, R. A., & Quintana, S. M. (2019). Timing of postpartum etonogestrel-releasing implant insertion and bleeding patterns, weight change, 12-month continuation and satisfaction rates: a randomized controlled trial. *Contraception*, *100*(4), 258–263. <https://doi.org/10.1016/j.contraception.2019.05.007> | Secondary analysis of open randomised controlled trail | 100 | Timing of postpartum insertion (<48 hours v >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 v delayed postpartum insertion have similar bleeding rates at 12 months. Amenorrhoea rates high in both groups. |
| Wahab, N. A., Rahman, N. A. A., Mustafa, K. B., Awang, M., Sidek, A. A., & Ros, R. M. (2016). A clinical evaluation of bleeding patterns, adverse effects, and satisfaction with the subdermal etonogestrel implant among postpartum and non-postpartum users. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, *132*(2), 237–238. <https://doi.org/https://dx.doi.org/10.1016/j.ijgo.2015.07.022> | Prospective cohort study. Not clear if randomisation occurred | 60 postpartum/ 50 non-postpartum | Postpartum v non-postpartum | 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 postpartum grouped at 6 months, and infrequent bleeding more common in non-postpartum |

### 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 months, 6 months, 12 months, or less than 36 months (see Table 3).

Additional data was sought from Lazorwitz (2019), Casey (2013), Bryant (2017) and DiCarlo (2014)9,11,12,14. Only Lazorwitz (2019) 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).

**Table 3. Risk of Bias Tables**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Robins 1 Non RCTs | Bias due to confounding | Bias due to selection of participants | Bias due to classification of interventions | Bias due to deviation from intended intervention | Bias due to missing data | Bias due to measurement of outcomes | Bias due to selective reporting of results | Overall |
|  |  |  |  |  |  |  |  |  |
| Casey 2011 | Serious | Moderate | Low | Unclear | Serious-missing data, data extraction by one reviewer only | Low (removed for bleeding or not) | Low | Serious |
| Casey 2013 | Moderate | Moderate | Low | Unclear | Low | Moderate | Low | Moderate |
| Crockett 2017 | Serious – statistically significant differences between inpatient and outpatient groups | Moderate | Low | Unclear | Low | Moderate | Low | Serious |
| DiCarlo 2015 | Low | Low | Low | Low | Low | Low | Low | Low |
| Green 2021 | Serious | Moderate | Moderate | N/A | Serious – missing and imputed data | Moderate | Moderate | Serious |
| Ireland 2014 | 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 2019 | 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 2016 | 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 |
| Petersen 2019 | Low | Moderate | Low | Not reported | Moderate - missing data <= 65 participants | Serious - assumed continuing with implant unless recorded (noted in limitations of paper) | Low | Serious |
| Rai 2004 | 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 2016 | Serious (no baseline demographic data and no corrections) | Low | Low -postpartum 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., 2017 | Low | Unclear | High | Unclear | High |
| Vieira et al., 2019 | Low | Low | Low | Unclear | Low |

Reporting Bias Assessment

Of the two RCTs one (Bryant 2017) scored ‘high’ overall RoB and one (Viera 2019) scored low overall RoB. For the non RCTs seven scored ‘serious’ overall RoB (Casey 2011, Crockett 2017, Ireland 2014, Obijuru 2016, Peterson 2019, Rai 2004, Green 2021), three scored ‘moderate’ (Casey 2013, Lazorwitz 2019, Wahab 2016) and one scored ‘low’ RoB (DiCarlo 2015; see Table 3).

Results of individual studies

BMI

BMI as a predictor was explored by six studies (Casey 2013, Casey 2011, Obijuru 2016, Lazorwitz 2019, Green 2021 & Di Carlo 2015) 11,12,14,17,18,21.

Green (2021), Casey (2013) and Di Carlo (2015) report that women with lower BMIs are significantly more likely to have unfavourable bleeding or removal due to bleeding.

Casey et al (2013) 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/m2 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/m2, 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 health care practitioner (24.6v27.0kg/m2, p=0.003) 11.

Di Carlo et al.(2015) 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 12. The study used the WHO definitions of bleeding/spotting and 90- day references periods 22 .

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 (24.84kg/m2) is higher than in the group of women with unfavourable bleeding (20.75 kg/m2) (p<0.005)(Di Carlo 2015) 12.

Green et al. (2021), 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 23.5kg.m2 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/m2 for those who had not (p=0.04) 17. There was no statistically significant difference detected in absolute weight (kg) between women with appointments for bleeding and those without.

Lazorwitz(2019), Obijuru (2016) and Casey (2011)report no significant association of BMI with various ‘unfavourable’ bleeding outcomes 14,21.

Casey et al (2011) carried out a retrospective review of 155 medical records with a primary outcome of requests for removal for bleeding changes and report the mean [SD] BMI of those with no Healthcare Provider (HCP) contact for bleeding (29.1kg [7.0]), with HCP contact for bleeding but no removal (28.0 kg [6.9]) and with removal for bleeding (25.8 kg [7.2]). The authors state that BMI was not a statistically significant risk for bleeding or implant removal (for any reason) 18.

Obijuru (2016) 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 (2019) et al. report on a cross-sectional prospective study whose primary outcome was the effect of 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 criteria14.

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 (Rai 2004, Casey 2013, Casey 2011, Lazorwitz 2019, Green 2021 & Di Carlo 2015) 11,12,14,17,18,20.

Lazorwitz (2019), Di Carlo (2014), Casey (2013), Casey (2011) and Rai (2004) report no association of age with ‘unfavourable’ bleeding or removal due to bleeding 11,12,14,20.

Rai 2004 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 (2013) 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 a 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 (2019) in a prospective, cross-sectional study primarily looking at etonorgestrel 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 (2015) 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=30.1years (SD 6.6)), p=0.27.

Casey (2011) 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)18.

Only Green (2019) 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) 17.

Post-partum insertion

Seven studies looked at post-partum insertion as a predictor, either as a primary or secondary variable (Wahab 2016, Ireland 2014, Viera 2019, Bryant 2017, Casey 2011, Casey 2013, Crockett et al., 2017) 9,10,13,16,18,19,23. None found statistically significant differences in unfavourable bleeding patterns between post-partum and non-post-partum insertion.

Wahab (2016), in a prospective cohort study, compared bleeding rates 3 months and 6 months after insertion between women who had an implant inserted within eight 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 delivery13.

Women were followed up at three and six 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 (2014), 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 hours) compared to delayed post-partum insertion (6-12 weeks) and non-postpartum placement (more than 12 weeks after delivery). The primary outcome was “% removed due to irregular bleeding” in each of the three groups16. No significant difference was found in percentage removal due to irregular bleeding between immediate (19.3%), delayed (18.4%) and interval (20.8%) insertions 16. No data was supplied on breastfeeding patterns in post-partum women, which is a limitation of the study.

Vieira et al (2019) performed a secondary analysis of an open randomised-controlled trial of 100 women receiving the ENG contraceptive implant either early postpartum (within 48 hours of delivery) or delayed postpartum (at 6 weeks post-partum) and reports similar bleeding rates for both groups at 3, 6, 9 and 12 months 10. Vieira et al (2019) 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. (2017) compared immediate (before hospital discharge) post-partum placement with delayed placement at 6 weeks in postpartum 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. (2013) found no association with post-partum placement and removal for bleeding (OR=1.5; 95% CI 0.8,3.0) 11. 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. (2017) conducted a retrospective cohort study for all women receiving the etonogestrel implant immediately postpartum (i.e. before postnatal discharge), delayed postpartum(<8 weeks after birth) or non-postpartum between July 1, 2007, and June 30, 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 months23. The study found a lower odds ratio 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 postpartum groups in this retrospective study.

Casey et al (2011) report that neither postpartum 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 (Petersen 2019, Di Carlo 2015, Rai 2014, Casey 2013, Casey 2011, Green 2021)11,12,15,17,18. Parity refers to any pregnancy beyond 24 weeks whilst gravidity refers to any pregnancy.

Two (Petersen 2019 and DiCarlo 2015) found an effect of gravidity or parity on reported bleeding but in opposite directions. The remaining four report no association.

Petersen et al (2019) in a retrospective cohort study of all 544 women receiving an implant at a USA 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 period15. 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. (2015) 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 patterns12. 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 Petersen, in that multiparity (i.e., higher gravidity) is associated with unfavourable bleeding.

Casey et al (2013) 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)11.

Rai 2004 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. (2011) report that parity, defined as >3 or <=3, was not a statistically significant risks for reported bleeding or implant removal (for any reason).18

Green (2021) 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 not17.

Tobacco use (Petersen 2019)

Petersen et al (2019) 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).15

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.

**Table 4. Data Extraction Table**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 4. Data Extraction Table** | | | | | | | | | | |
| **Author Date** | **Predictor** | **Outcomes** |  |  |  |  |  |  |  |  |
| Casey 2011 | 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 2013 | 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 2015 | 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 2021 | BMI |  | **Bleeding appointment (n=268)** | **No bleeding appointment (n=932)** |  |  |  |  |  |  |
|  |  | **Median BMI** | 23.5 | 24.2 |  |  |  |  |  |  |
| Lazorwitz 2019 | 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 2016 | 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 2011 | 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 2013 | 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 2015 | Age |  | **Favourable bleeding** | **Unfavourable bleeding** |  |  |  |  |  |  |
|  |  |  | **>50% RPs 6-12 months** | **>50% RP -6-12 months)** |  |  |  |  |  |  |
|  |  | **Mean Age** | 32.3 | 30.1 |  |  |  |  |  |  |
|  |  | **SD** | 7.4 | 6.6 |  |  |  |  |  |  |
| Green 2021 | Age |  | **Bleeding appointment (n=268)** | **No bleeding appointment (n=932)** |  |  |  |  |  |  |
|  |  | **Median Age** | 18.9 | 19.4 |  |  |  |  |  |  |
| Lazorwitz 2019 | 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 2004 | 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 2011 | Postpartum v non-postpartum |  | **No HCP contact for bleeding** | **HCP contact for bleeding but not removed** | **Removed for bleeding** | *Totals* |  |  |  |  |
|  |  | **N** | 113 | 19 | 23 |  |  |  |  |  |
|  |  | **Postpartum placement** | 30 | 8 | 9 | *47* |  |  |  |  |
|  |  | ***Non-postpartum placement*** | *83* | *11* | *14* | *108* |  |  |  |  |
|  |  | **Breast feeding** | 21 | 5 | 3 | 29 |  |  |  |  |
| Casey 2013 | Postpartum v non-postpartum |  | **No HCP contact for bleeding** | **HCP contact for bleeding but not removed** | **Removed for bleeding** | Totals |  |  |  |  |
|  |  | **N** | 211 | 43 | 50 | 304 |  |  |  |  |
|  |  | **Postpartum** | 55 | 10 | 16 | 81 |  |  |  |  |
|  |  | ***Non-postpartum*** | *156* | *33* | *34* | *223* |  |  |  |  |
|  |  | **Lactating at placement** | 30 | 2 | 10 | 42 |  |  |  |  |
|  |  | **Not lactating at placement** | 167 | 39 | 39 | 245 |  |  |  |  |
|  |  | **Lactation status unknown** | 14 | 2 | 1 | 17 |  |  |  |  |
| Crockett 2017 | Postpartum v non-postpartum |  | **Removal due to bleeding by 12 months:** | **Removal due to bleeding by 6 months:** |  |  |  |  |  |  |
|  |  | **Interval:** | 16/275 | 6/319 |  |  |  |  |  |  |
|  |  | **Postpartum (immed+ delayed < 8 weeks):** | 16/243 | 12/457 |  |  |  |  |  |  |
|  |  | *Totals N* | 32/518 | 18/776 |  |  |  |  |  |  |
| Ireland 2014 | Postpartum v non-postpartum |  | **Implant removed for bleeding < 36 months (YES)** | **Implant removed for bleeding < 36 months (NO)** |  |  |  |  |  |  |
|  |  | **Immediate Postpartum (n)** | 50 | 209 |  |  |  |  |  |  |
|  |  | **Delayed post-partum (n)** | 9 | 40 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  | **Interval (n)** | 22 | 84 |  |  |  |  |  |  |
|  |  | **Totals** | 81 | 313 | **Total =414** |  |  |  |  |  |
| Wahab 2016 | Postpartum v non-postpartum | **Bleeding pattern at 6 months follow up duration** |  |  |  |  |  |  |  |  |
|  |  |  | **Amenorrhoea** | **Infrequent** | **Normal** | ***Favourable i.e. Amenorrhoea, Infrequent, Normal*** | **Frequent** | **Prolonged** | ***Unfavourable i.e. Frequent, prolonged*** |  |
|  |  | **Postpartum (N)** | 39 | 5 | 7 | *51* | 6 | 3 | *9* |  |
|  |  | **Non-postpartum (N)** | 19 | 12 | 8 | *39* | 8 | 3 | *11* |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Bryant 2017 | Immediate postpartum v delayed postpartum |  | **Heavier, prolonged bleeding or cramps at 12 months** | **Removed due to bleeding before 12 months** | *Totals* |  |  |  |  |  |
|  |  | **Immediate postpartum insertion (n=37)** | 25 | 3 | 28/37 |  |  |  |  |  |
|  |  | **Delayed postpartum insertion at 6 weeks (n=27)** | 18 | 0 | 18/27 |  |  |  |  |  |
| Crockett 2017 | Immediate v delayed postpartum |  | **Removal due to bleeding by 6 months N=457** |  | **Removal due to bleeding by 12 months N=243** |  |  |  |  |  |
|  |  | **Immediate postpartum (inpatient): n=342** | 9 | **Immediate postpartum (inpatient): n=139** | 7 |  |  |  |  |  |
|  |  | **Delayed postpartum <8 weeks: n=115** | 3 | **Delayed postpartum <8 weeks: n=104** | 9 |  |  |  |  |  |
|  |  | *Totals* | *12/457* |  | *16/243* |  |  |  |  |  |
| Ireland 2014 | Immediate postpartum v delayed postpartum |  | **Implant removed for bleeding before 36 mths YES** | **Implant removed for bleeding before 36 mths NO** | Totals |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  | **Immediate Postpartum (<96hrs)** | 50 | 209 | 259 |  |  |  |  |  |
|  |  | **Delayed postpartum (6-12 weeks)** | 9 | 40 | 49 |  |  |  |  |  |
|  |  | *Interval* | *22* | *84* | *106* |  |  |  |  |  |
|  |  |  |  |  | **414** |  |  |  |  |  |
| Viera 2019 | Immediate v delayed postpartum |  | **Bleeding pattern at RP4: 12 months** |  |  |  |  |  |  |  |
|  |  |  | **Amenorrhoea** | **Infrequent** | **Normal** | ***Favourable i.e. Amenorrhoea, Infrequent, Normal*** | **Frequent** | **Prolonged** | ***Unfavourable i.e Frequent, prolonged*** | **Missing** |
|  |  | **Early postpartum (48 hrs)** | 26 | 11 | 3 | 40 | 4 | 1 | 5 | 6 |
|  |  | **Delayed Postpartum (6weeks)** | 23 | 7 | 6 | 36 | 5 | 1 | 6 | 9 |
|  |  |  | **Bleeding pattern at RP2: 6 months** |  |  |  |  |  |  |  |
|  |  |  | **Amenorrhoea** | **Infrequent** | **Normal** | ***Favourable i.e. Amenorrhoea, Infrequent, Normal*** | **Frequent** | **Prolonged** | ***Unfavourable i.e Frequent, prolonged*** | **Missing** |
|  |  | **Early postpartum (48 hrs)** | 26 | 7 | 2 | *35* | 7 | 1 | *8* | 8 |
|  |  | **Delayed Postpartum (6weeks)** | 28 | 11 | 2 | *41* | 3 | 1 | *4* | 6 |
|  |  |  |  |  |  |  |  |  |  |  |
| Casey 2011 | 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 2013 | 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 2015 | 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 2021 | Parity/Gravidity |  | **Bleeding appointment (n=268)** | **No bleeding appointment (n=932)** |  |  |  |  |  |  |
|  |  | Nulligravid | 74.30% | 72.40% |  |  |  |  |  |  |
|  |  | Nulliparous | 77.20% | 77.90% |  |  |  |  |  |  |
| Petersen 2019 | 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 2004 | 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 |  |  |  |  |  |  |

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 (2019) and Wahab (2017), but ‘Favourable’ and ‘Unfavourable’ bleeding patterns had to be calculated, extrapolated, or estimated for Lazorwitz (2019), Casey (2013), Casey (2011), Bryant (2017) and Obijuru (2016)9–11,13,14,18,21. The period in which bleeding complaints were reported varied between 6 months after insertion to 36 months. Di Carlo (2015) 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’12.

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( 2021) 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 years17.

None of the seven studies which assessed or reported the effect of postpartum status showed an effect on bleeding pattern9–11,13,16,18,19. 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 women11,18. In one of these (Casey 2013), a retrospective study, breastfeeding at the time of insertion is recorded but not at the time of reported bleeding complaints11. In an earlier study by the same authors (Casey 2011) breastfeeding is recorded but no indication is given about whether breastfeeding was at the time of insertion or at the time of reported bleeding complaints18. 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 etonorgestrel Implant in the postpartum 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 (2019) but high in Bryant(2017), due to missing data, and uncertainty in terms of measurement of the outcome, because bleeding patterns were a secondary outcome9,10.

In the non-RCTs, the risk of bias is moderate to serious in all but Di Carlo(2015), due to the retrospective nature of the studies (Casey 2011, Obijuru, 2016, Crockett 2017, Green 2021 & Rai 2004), differences between groups at baseline, (Crockett 2017, Ireland 2014, Green 2021), missing data (Casey 2011, Obijuru 2016, Rai 2004, Petersen 2019, Green 2021 & Ireland 2014) or inexact measurement and/or reporting of the outcomes of interest (Rai 2004, Petersen 2019, Obijuru 2016, Green 2021 & Lazorwitz 2019).

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 20196. ‘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 e.g., ‘Health Care 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 2008 (see above) and so were unable to include a significant amount of data which would have fitted our inclusion criteria3.

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. 2008, who report a highly significant negative correlation between BMI and mean number of bleeding days per reference period (r=-1.772, p<0.0001)8. In keeping with our findings, Mansour et al. 2008 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.

Postpartum 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 etonorgestrel 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 postpartum 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 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.

### Registration of Review Protocol

This review was registered with Prospero CRD Register on 27-04-21 Reg No. CRD42021240859. <https://www.crd.york.ac.uk/prospero/>

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### Data

Data availability statement – this paper did not produce any new data.

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*Figure Legends*

Figure 1. Prisma Diagram