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REVIEW ARTICLE

Gynecology

Postpartum contraception: A matter of guidelines

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Abstract

The postpartum period is the perfect time to access family planning services. WHO guidelines contraindicate combined hormonal contraceptives postpartum in breastfeeding patients between 6 weeks and 6 months after delivery (Medical Eligibility Criteria category 3). On the contrary, the Faculty of Sexual and Reproductive Healthcare and the Centers for Disease Control and Prevention guidelines do not contraindicate their use in women who breastfeed from 6 weeks to 6 months postpartum. New combined hormonal contraceptives with natural estrogens have never been studied in this setting. Guidelines agree on the prescription of the progestin-only pill postpartum in non-breastfeeding women (category 1). Differences are found in women who breastfeed. In non-breastfeeding women, an implant is considered safe (category 1) by all guidelines, without any distinction in time. Regarding postpartum breastfeeding women, the guidelines for implants give quite different indications but are still permissive. Intrauterine devices are viable options for postpartum contraception but guidelines give different indications about the timing of insertion. Postplacental intrauterine device placement can reduce the subsequent unintended pregnancy rate, particularly in settings at greatest risk of not having recommended postpartum controls. However, it has yet to be understood whether this approach can really have an advantage in high-income countries. Postpartum contraception is not a 'matter of guidelines': it is the best customization for each woman, as early as possible but at the ideal timing.

KEYWORDS
breastfeeding, contraception, intrauterine device, long-acting reversible contraception, postpartum period, subcutaneous implant, thrombosis

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; CDC, Centers for Disease Control and Prevention; CHC, combined hormonal contraception; DRSP, drospirenone; E2, estradiol; E2V, estradiol valerate; E4, estetrol; ETN, etonogestrel; FSRH, Faculty of Sexual and Reproductive Healthcare; IPI, interpregnancy intervals; IUD, intrauterine device; IUS, intrauterine system; LAM, lactational amenorrhea; LNG, levonorgestrel; MEC, medical eligibility criteria; POP, progestin-only pill; RCT, randomized controlled trial; VTE, venous thromboembolism.

1 | INTRODUCTION

Postpartum is the perfect moment to access family planning services. The contraceptive choice should be evaluated with the woman before she leaves the hospital, but it is even better if she is evaluated during pregnancy. Contraceptive counseling involves understanding a woman's wishes for future pregnancies, her preferences regarding available contraceptive options, and the characteristics of the contraceptive methods.

Clinicians should adopt a person-centered approach; in addition, some medical considerations are indispensable, including the timing of initiation, medical comorbidities, and breastfeeding status, as well as social and cultural factors.

Shorter interpregnancy intervals (IPI) are related to adverse maternal, perinatal, and infantile outcomes.[1] Indeed, WHO recommends an interval of at least 24 months[2] between subsequent pregnancies. Similarly, the American College of Obstetricians and Gynecologists (ACOG) advises women to avoid an IPI of less than 6 months and to be informed about the risks and benefits of an IPI shorter than 18 months.[3] The Faculty of Sexual and Reproductive Healthcare (FSRH) reports that an IPI shorter than a year between delivery and a new conception is related to an increased risk of preterm delivery and small-for-gestational-age neonates.[4,5]

For this reason, it is essential to evaluate the best timing of the initiation of postpartum contraception according to different international guidelines. Furthermore, breastfeeding and the postpartum thromboembolic risk are important factors to consider when choosing a specific hormonal contraceptive during this period of a woman's life.

The aim of this narrative review is to compare guidelines published by international recognized scientific societies on postpartum contraception, to gain an up-to-date overview of this topic, keeping the focus on each patient's needs, and to facilitate an individualized and supported choice.

2 | COMBINED HORMONAL CONTRACEPTIVE (CHC)

2.1 | Comparison of guidelines on CHCs in breastfeeding

The fifth edition of the WHO guidelines was published in 2015.[6] According to these guidelines, for breastfeeding women, it is recommended to avoid CHC use within 6 weeks of delivery. Moreover, women who breastfeed should not use CHCs between 6 weeks and 6 months after giving birth. Breastfeeding women who have given birth more than 6 months previously can generally use CHCs. In non-breastfeeding women, CHCs should not be used within 21 days of delivery. Between 21 and 42 days postpartum, women with other risk factors for venous thromboembolism (VTE) should not use CHC methods. Non-breastfeeding patients can use CHCs 21 days after delivery, if they have no other risk factors for VTE. The additional reported risk factors for VTE are immobility, blood transfusion at delivery, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) greater than 30, cesarean section, postpartum hemorrhage, pre-eclampsia, or smoking. Forty-two days after giving birth, non-breastfeeding women can use CHCs without restrictions.

The US Medical Eligibility Criteria (MEC)[7] Chart for Contraceptive Use was updated by the Centers for Disease Control and Prevention (CDC) in 2020. According to these guidelines, CHCs can be initiated in breastfeeding women 30 days after delivery in the absence of other risk factors for VTE or 6 weeks after delivery in their presence (see above). In women who are not breastfeeding, CHCs can be started 3 weeks postpartum where there are no other risk factors for VTE or 6 weeks after delivery with other risk factors.

According to the FSRH 2020 guidelines (Contraception After Pregnancy; UK MEC),[5,8] CHCs should not be used until 42 days after delivery in breastfeeding women or in those who are not breastfeeding but have other VTE risk factors (see above). Women without other risk factors for VTE who are not breastfeeding may consider using CHCs starting 3 weeks after delivery. CHCs can be offered to suitable women where other methods are unsuitable, unacceptable, or unavailable. There are potential significant health risks associated with CHC use in the immediate postpartum period; therefore, careful blood pressure and BMI measurements should be routinely performed and women should be adequately informed of the risks.[5,9,10]

The above guidelines are mostly aligned with each other. However, a few, but substantial, differences are evident. In fact, WHO guidelines contraindicate CHCs postpartum in breastfeeding patients between 6 weeks and 6 months after delivery (MEC category 3). On the contrary, the FSRH and CDC guidelines do not contraindicate the use of CHCs in patients who breastfeed from 6 weeks to 6 months postpartum (MEC category 2). In breastfeeding women, in this specific early postpartum period, the use of modern CHCs containing natural estrogens, such as estradiol (E2), estradiol valerate (E2V), or estetrol (E4), might be preferred, although nothing has been published. All MEC categories of the different guidelines are shown in Table 1.

2.2 | Effect of CHCs use on breastfeeding

Prolactin promotes milk production during breastfeeding. During pregnancy, estrogens and progesterone inhibit the effects of prolactin. After giving birth, the drop in progesterone triggers prolactin to start milk production. Even breastfeeding itself, by stimulating the production of oxytocin and prolactin, favors the production of milk.[11]

The early administration of contraceptives that contain estrogen and progestins could theoretically slow down or block the mechanism that triggers milk production. The effects of CHCs on breastfeeding are debated. In addition, some of the topics of interest expand on the potential effects of steroid hormones on the development and growth of neonates who are breastfed. However, several

TABLE 1 Postpartum combined hormonal contraceptive use:[5–8,10] A matter of guidelines.

	WHO 2015		UK 2019		US 2020	
Postpartum (breastfeeding women)	<21 days	4	<21 days	4	<21 days	4
	21–42 days	4	21–42 days	4	21–30 days	3
					30–42 days[a]	3
					30–42 days	2
	≥6 weeks <6 months	3	≥6 weeks <6 months	2	≥6 weeks	2
	≥6 months	2	≥6 months	1		
Postpartum (non-breastfeeding women)	<21 days	3	<21 days	3	<21 days	4
	<21 days[a]	4	<21 days[a]	4		
	21–42 days	2	21–42 days	2	21–42 days	2
	21–42 days[a]	3	21–42 days[a]	3	21–42 days[a]	3
	>6 weeks	1	>6 weeks	1	>6 weeks	1

[a]With other risk factors for venous thromboembolism (immobility, transfusion at delivery, body mass index, (calculated as weight in kilograms divided by the square of height in meters) >30, postpartum hemorrhage, immediately post-cesarean delivery, pre-eclampsia or smoking, use of combined hormonal contraceptives may pose an additional increased risk for venous thromboembolism).

studies in the literature have shown that the hormonal levels passed to the neonate during breastfeeding are minimal and that hormonal contraceptives do not adversely affect the growth or well-being of neonates.[12,13] Some authors have estimated that a fully breastfed neonate whose mum takes 50 μg of ethinyl estradiol per day receives a dose of ethinyl estradiol of about 10 ng per day.[14,15] Some studies have reported a negative effect on the amount of milk produced in patients taking CHCs.[16] In this field, it would be interesting to study the specific effects of E2, E2V, or E4 containing new CHCs on the growth or health of neonates. Other studies have not reported a substantial difference in the effect on infants of the use of medroxyprogesterone acetate.[17]

The literature on this topic is very conflicting and not equivocal, both on the effect of CHCs on breastfeeding and on infantile outcomes; therefore, it needs further study[18–20] and a renewed interest.

2.3 | Thromboembolic risk of CHCs

The use of any CHC can increase the VTE risk if compared with non-use, especially in the postpartum period, the most thrombogenic period ever in a woman's life. Products that contain low dose ethinyl estradiol (less than 50 μg) in combination with levonorgestrel (LNG), norgestimate, or norethisterone are related to a lower VTE risk. The decision to use any product other than low risk ones should be taken after counseling with the woman.[21] The estrogenic component of CHCs remained unchanged for a long time and most contained ethinyl estradiol. However, over the years, natural estrogens (E2, E2V, E4) have been introduced to personalize and improve the tolerability of CHCs.[22]

Commercial natural estrogens (E2, E2V, E4) have a lower oral bioavailability and are metabolized more rapidly than ethinyl estradiol, due to the absence of an ethinyl group.

CHCs containing ethinyl estradiol can enhance some coagulation factor activity by about 30%–50%, whereas there is a decrease in the activity of natural anticoagulants of about 30%–40% at the same time.[23] The resulting state of hypercoagulability appears to be independent of the way of administration of the ethinyl estradiol, but dose dependent with a direct correlation.[24] Furthermore, the risk also depends on the type of progestin.[25,26] Replacement with oral E2 may reduce, but not completely avoid, the impact on the coagulation cascade of CHCs; in fact, the effect of ethinyl estradiol for protein synthesis on the liver (e.g. angiotensinogen, sex hormone binding globulin and corticosteroid binding globulin) is up to 500–600 times greater than during E2 use.[27,28]

According to the European Medicines Agency data, the risk of VTE in women taking CHCs ranges from five to 12 cases per 10000 women/year, in comparison with two cases of VTE per 10000 women/year in women not using CHCs,[21,28] 10 cases during pregnancy, and 50 during puerperium per 10000 women/year. Some studies have shown that combinations containing natural estrogens (E2, E2V, E4) have a similar (sometimes lower) cardiovascular risk compared with CHCs containing LNG.[29,30] Moreover, some preliminary studies have shown changes in hemostasis parameters after six treatment cycles with E4/drospirenone (DRSP), similar to those observed with ethinyl estradiol/LNG.[31]

Furthermore, the non-oral administration of E2 (intravaginal or transdermal) could allow the use of smaller quantities of E2 necessary to give satisfactory control of the menstrual cycle. Until now, the commercial intravaginal and transdermal contraceptives exclusively contained ethinyl estradiol, with devices containing E2 having also been studied in recent years.[32,33]

Some physiologic hematologic changes occurring during pregnancy are the increase in levels of coagulation factors and fibrinogen, the decrease in the concentrations of natural anticoagulants such protein S and activated protein C status, and the shift in coagulation and fibrinolytic systems towards hypercoagulability.

Most increased factors, such as factor VIII, factor X, fibrinogen, and plasminogen activator inhibitors 1 and 2, can return to normality within 1–4 weeks postpartum, whereas others (factor VII, D-dimer, protein S, activated protein C, prothrombin fragments 1 and 2) may take 6 or 8 weeks to return to normal values. Although this sophisticated mechanism prevents hemorrhage at delivery, it greatly increases the risk of VTE, both VTE and pulmonary embolism, during pregnancy and especially in the puerperium. In addition, increasing venous stasis during pregnancy (the 30% reduction in flow observed at 15 gestational weeks increases to more than 60% by 36 weeks) and vascular damage sustained during delivery place postpartum women at a significantly higher risk of developing VTE. Women present a 22- to 84-fold increased risk during the first 6 weeks postpartum when compared with non-pregnant, non-postpartum reproductive age women; the incidence rates of VTE range from 25 to 99/10 000 women/year.

The risk of VTE during the postpartum period is most pronounced around the time of delivery and may be increased by various factors (see above). Some postpartum women may have multiple factors and these risk factors can be additive, increasing their overall risk several folds. Those women with congenital thrombophilia or who have suffered a previous VTE episode are at even higher risk, needing a specific anticoagulant therapy.

However, the increased risk associated with the postpartum period declines rapidly in the first 21 days after delivery, returning to near baseline levels by 42 days, reflecting the normalization of coagulation factors and venous flow.

Therefore, the relative risk of VTE increased approximately five-fold in pregnancy and 60-fold in the postpartum period, particularly during the first 3 weeks.[34] Therefore, for thromboembolic risk, CHCs are contraindicated in the first postpartum weeks, as reported in the three guidelines, albeit with some substantial differences (Table 1).

3 | BREASTFEEDING AS A CONTRACEPTIVE

The method of lactational amenorrhea (LAM) is a natural contraceptive method. This method is based on the spontaneous anovulation that occurs in breastfeeding women, but requires exclusive and frequent breastfeeding. The time between feedings should not exceed 4 h during the day or 6 h at night. There are no health risks or adverse effects to using LAM, but this method can only be used for 6 months after giving birth or until the woman's period returns.[35] If correctly used, the Pearl Index of LAM is approximately 1%–2%.[36,37]

Non-breastfeeding women should be advised that a new pregnancy can occur within the first 2 months after delivery without contraception.

In breastfeeding women, gonadotropins are suppressed due to the high concentrations of circulating prolactin. The suppression of ovarian function depends on the actual breastfeeding behavior: frequent sucking, even at night, prolongs ovarian inhibition. The introduction of formula milk and/or solid meals is associated with a reduction in the frequency and duration of breastfeeding activity. Therefore, the suppressive effect of breastfeeding decreases and ovarian activity could resume. The formalized LAM recommends starting another additional contraceptive method when the infant is 6 months old, or earlier if menses return or exclusive breastfeeding stops.[34]

4 | PROGESTIN-ONLY PILL (POP)

The safest hormonal contraceptive steroid in the postpartum period remains progestin and the POP is a viable option for the immediate postpartum period.

As can be seen in Table 2, guidelines agree on the prescription of POPs postpartum in non-breastfeeding women, considering

TABLE 2 Postpartum progestin-only pill use:[5–8,10] A matter of guidelines.

	WHO 2015		UK 2019		US 2020	
Postpartum (breastfeeding women)					<21 days	2
					21–30 days[a]	2
					30–42 days[a]	1
	<6 weeks	2	<6 weeks	1		1
	≥6 weeks <6 months	1	≥6 weeks <6 months	1	>42 days	
	≥6 months	1	≥6 months	1		
Postpartum (non-breastfeeding women)	<21 days	1	0–3 weeks	1	<21 days	1
	≥21 days	1	3–6 weeks[b]	1	21–42 days[a]	1
			≥6 weeks	1	>42 days	1

[a]With other risk factors for venous thromboembolism (e.g. age ≥ years, previous venous thromboembolism, thrombophilia, immobility, transfusion at delivery, peripartum cardiomyopathy, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) ≥30, postpartum hemorrhage, post-cesarean delivery, pre-eclampsia, or smoking).

[b]Other risk factors for venous thromboembolism, such as immobility, transfusion at delivery, BMI > 30, postpartum hemorrhage, immediately post-cesarean delivery, pre-eclampsia or smoking, may pose an additional increased risk for venous thromboembolism.

TABLE 3 Postpartum implant use:[5–8,10] A matter of guidelines.

	WHO 2015		UK 2019		US 2020	
Postpartum (breastfeeding women)					<21 days	2
					21–30 days[a]	2
					30–42 days[a]	1
	<6 weeks	2	<6 weeks	1		1
	≥6 weeks <6 months	1	≥6 weeks <6 months	1	>42 days	
	≥6 months	1	≥6 months	1		
Postpartum (non-breastfeeding women)	<21 days	1	0–3 weeks	1	<21 days	1
	≥21 days	1	3–6 weeks[b]	1	21–42 days[a]	1
			≥6 weeks	1	>42 days	1

[a]With other risk factors for venous thromboembolism (e.g., age ≥ years, previous venous thromboembolism, thrombophilia, immobility, transfusion at delivery, peripartum cardiomyopathy, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) ≥30, postpartum hemorrhage, post-cesarean delivery, pre-eclampsia, or smoking).

[b]Other risk factors for venous thromboembolism, such as immobility, transfusion at delivery, BMI > 30, postpartum hemorrhage, immediately post-cesarean delivery, pre-eclampsia or smoking, may pose an additional increased risk for venous thromboembolism.

it completely safe with no time limit (category 1). Differences are found in women who breastfeed, particularly in the first 4–6 weeks after delivery. The UK guidelines do not indicate any restrictions: breastfeeding in the postnatal period is not a limiting factor for starting POP use (category 1).[5,8] WHO remains cautious in women who breastfeed within 4 weeks after delivery (category 2), recommending that breastfeeding women do not use progestin-only contraceptives prior to 6 weeks postpartum, except those at risk for morbidity or mortality during pregnancy and with limited access to health services.[6] The US guidelines extend the period to 6 weeks (category 2): for both guidelines, however, even in this category of women, the benefits still outweigh the risks.[7]

Several trials have been performed in order to study the effect of the POP in the postnatal period on breastfeeding. Dutta and Dutta[38] performed a prospective clinical trial on lactating women starting a POP (desogestrel 75 μg/day) 6 weeks after delivery for 6 months to determine the safety, effectiveness, and tolerability of the drug: they concluded that the drug had good tolerability, good efficacy, and good safety and did not affect the growth and development of breastfed infants. Phillips et al.[39] conducted a systematic review for the WHO's MEC and evaluated the effects of POPs on neonatal outcomes (breastfeeding performance, infant growth, development and health). Consistent evidence, largely from fair or poor-quality observational studies, suggests that POPs, when used by breastfeeding women, do not compromise their ability to breastfeed. Across all observational and randomized studies, the evidence that POPs do not adversely affect infant growth, well-being, or development during the first year of life is generally consistent: these findings were then incorporated into the last update of the MEC.[6] The review conducted by Kapp et al.[40] on the use of POPs in postpartum breastfeeding women came to the same conclusions.

The effects of POPs containing desogestrel in the postpartum period have been extensively studied. However, little has been found in the literature about the new progestin-only, estrogen-free contraceptive, DRSP, in a dosage of 4 mg/day in a 24/4 regimen (Slinda, Exeltis®, Argentina). Only one study has assessed the passage of DRSP into breast milk after the single-dose administration of a combined oral contraceptive containing ethinyl estradiol and DRSP. Assuming a daily ingestion of approximately 800 mL breast milk, the daily dose passing to the infant through breast milk is estimated to be approximately 3 μg DRSP.[41] Melka et al.[42] conducted a recent, open-label, non-comparative single-center study to evaluate the safety of the new POP containing 4 mg DRSP in breastfeeding women. The pill was administered for 7 days to achieve a steady-state concentration to the 12 selected subjects to assess the transfer of DRSP to breast milk. The pharmacokinetic parameters of DRSP in serum and in breast milk were in a similar range to previous single oral dose studies of 3 mg DRSP +30 μg ethinyl estradiol, indicating that lactation does not influence the pharmacokinetics of the steroid.[43] The amount of DRSP transferred to the infant by breast milk has been calculated based on the average concentration of DRSP found in breast milk 24 h after tablet administration and the same milk volume (800 mL) known to be ingested by a 2- to 5-month-old infant. In this study, the quantity of DRSP passing to the breast milk was 4478 ng during a period of 24 h, 0.11% of the maternal daily dose. Thus, at the doses of the product approved, no effects on breastfed newborns are expected.

5 | LONG-ACTING REVERSIBLE CONTRACEPTION

5.1 | Implant

The progestin-releasing subcutaneous implant is among the long-acting methods that can be used in the postpartum period. Its use is now common 4–8 weeks after delivery: in the literature, in fact, there are many studies on its "standard use" (4–8 weeks after

delivery), while a few studies have been conducted on the safety of its "early use" (before 4 weeks after delivery). Also, the guidelines differ regarding "early use".

Table 3 compares the different guidelines.[5–8] In women who are not breastfeeding, the implant is considered safe (category 1) by all three guidelines, without any distinction in time. Regarding breastfeeding women, the guidelines give different indications. The UK-MEC considers the use of the implant safe in breastfeeding women, even in the immediate postpartum period (within 6 weeks of delivery). The WHO-MEC and US-MEC, on the other hand, introduce a time distinction: on late use, they agree to total safety, whereas within 6 weeks (WHO) and within 30 days (US) they are more cautious (category 2), while still not contraindicating its use.

Several studies have been published on the tolerance of subcutaneous implant use in the postpartum period in comparison with standard use. Phemister et al.[44] conducted a prospective randomized study to demonstrate the safety of the implant's insertion immediately postpartum. Women reported possible adverse effects and acceptability in a diary during the time between the hospital visit and the follow-up visit. Compared with the group that received the implant after 4–6 weeks, women who received the Norplant® immediately reported no difference in blood pressure and weight, or the incidence of adverse effects. The immediate insertion group reported only significantly more headaches (15.1% vs. 2.8%, $P<0.01$) and acne occurrence (18.9% vs. 6.4%, $P<0.01$). In addition, more bleeding days were observed when LNG-releasing implants were inserted prior to 48 h after delivery, when compared to the insertion at 4–6 weeks. However, hemoglobin levels between the two groups were similar, so the clinical meaning of these results should be discussed.

Studies have also been conducted to assess the hemostatic and metabolic safety profile of insertion in the immediate postpartum period, although they are progestin-only contraceptive methods.

Brito et al.[45] designed a randomized controlled trial (RCT) to evaluate the effect of the etonorgestrel (ETN)-releasing implant inserted immediately, showing no effect on markers of coagulation cascade activation and no effects on maternal hemostasis. Another prospective randomized open pilot study demonstrated similar safety regarding the maternal metabolic profile.[46]

The ACOG's Committee on Obstetric Practice[47] states that "the contraceptive implant may be inserted in the delivery room or at any other time during the woman's stay in the postpartum unit before hospital discharge. There are no contraindications or risks specific to the postpartum period except for theoretical issues related to breastfeeding".

Some animal data suggest a possible effect of progesterone on the developing brain; however, whether similar effects can occur following progestin exposure in humans is unclear.[48–50] The use of ETN implants has been studied in breastfeeding women. No change in the volume or composition of breast milk was noted in these women, with no evident effects associated with the small levels of ETN ingested by the infants.[51] As WHO guidelines emphasize, "direct evidence demonstrates no harmful effect of progestin-only contraceptive initiation at ≤6 weeks postpartum on breastfeeding performance and generally demonstrates no harmful effects on neonate growth, health or development in the first year postpartum". However, all these studies were of poor quality, lacked standard definitions of breastfeeding or outcome measures, and were inadequately designed to determine whether a risk of long-term effects exist.[39,52] Gurtcheff et al.[53] studied the effects on a woman's ability to breastfeed newborns following early (1–3 days) compared with standard (4–8 weeks) insertion of an implant, with breastfeeding outcomes being similar. Henkel et al.[54] studied the effects of even earlier insertion on lactogenesis; through a non-inferiority RCT, they concluded that delivery room insertion (0–2 h postpartum) of the ETN implant does not delay the onset of lactogenesis when compared with initiation later in the hospitalization (24–48 h postpartum).

Another interesting aspect emerging from another study[53] is the importance of providing effective contraception before discharge, particularly in women who are unlikely to present themselves at the postpartum visit. This RCT emphasized the importance of early versus standardized insertion in the group of women analyzed: one-third of women randomly assigned to standard insertion never received their implants compared with just 3% of those who were randomly assigned to early insertion, despite being enrolled in a study in which they were consistently reminded, rescheduled as desired, and offered incentives. The short-term effect on the initiation of contraception is proven, as is also evident from the Cochrane review conducted by Sothornwit et al.;[55] evidence indicates that the rate of initiation of contraceptive implant at the first postpartum check-up visit was higher with immediate postpartum insertion than with delayed insertion. The long-term effects, on the other hand, are somewhat more controversial: there appeared to be little or no difference between the groups in the continuation of contraceptive implant use at 6 months and it was unclear whether there was any difference between the groups in the continuation rate or in the unintended pregnancy rate at 1 year.

5.2 | Intrauterine devices (IUDs)

It is now well known that IUDs, both hormonal (LNG-releasing intrauterine systems; LNG-IUS) and non-hormonal (copper-based), are viable options for postpartum contraception. The biggest debate, which is still open, is on the timing of the insertion; even international guidelines give different indications, especially regarding the immediate postpartum period.

As can be seen in Tables 4 and 5, all guidelines agree on the insertion of the IUD, both medicated and non-medicated, 4 weeks after delivery, with no contraindications (category 1). The only exception is puerperal sepsis: theoretical concern exists that postpartum insertion of an IUD in the case of recent chorioamnionitis or current endometritis might be associated with increased complications.

WHO[6] and UK[5,8] guidelines set 48 h after delivery as the safe time limit; within 48 h, insertion of the IUD is safe (category 1) (both

TABLE 4 Postpartum levonorgestrel intrauterine system use:[5–8,10] A matter of guidelines.

WHO 2015			UK 2019		US 2020		
<48 h[a]	Breastfeeding	2	<48 h[a]	1	<10 min	Breastfeeding	2
	Non-breastfeeding	1				Non-breastfeeding	1
≥48 h to 4 weeks		3	≥48 h to <4 weeks	3	≥10 min to <4 weeks		2
≥4 weeks		1	≥4 weeks	1	≥4 weeks		1
Postpartum sepsis		4	Postpartum sepsis	4	Postpartum sepsis		4

[a]Including insertion immediately after delivery of the placenta.

TABLE 5 Postpartum copper intrauterine device use:[5–8,10] A matter of guidelines.

WHO 2015		UK 2019		US 2020	
<48 h[a]	1	<48 h[a]	1	<10 min	1
≥48 h to <4 weeks	3	≥48 h to <4 weeks	3	≥10 min to <4 weeks	2
≥4 weeks	1	≥4 weeks	1	≥4 weeks	1
Postpartum sepsis	4	Postpartum sepsis	4	Postpartum sepsis	4

[a]Including insertion immediately after delivery of the placenta.

hormonal and non-hormonal IUDs). The only difference is that WHO remains cautious in breastfeeding women, assigning category 2 for medicated IUDs. The US guidelines are more restrictive: within 10 minutes postpartum, insertion is totally safe (category 1), except for the hormonal IUD in breastfeeding women (category 2), whereas from 10 minutes to 4 weeks postpartum, the benefits still outweigh the risks, even though they are not totally absent (category 2).

According to WHO guidelines, "immediate postpartum Cu-IUD insertion, particularly when insertion occurs immediately after delivery of the placenta, is associated with lower expulsion rates than delayed postpartum insertion. Additionally, postplacental placement at the time of cesarean section has lower expulsion rates than postplacental vaginal insertions. Insertion complications of perforation and infection are not increased by IUD placement at any time during the postpartum period".[6]

On the other hand, US guidelines specify that immediate postplacental (<10 min) and early postpartum (from 10 min up to 72 h) placement of copper IUDs and LNG-IUSs are related to an increased risk for expulsion compared with a normal placement. Early postpartum placement confers a similar or increased risk for expulsion, if compared with immediate postplacental placement. Although immediate postplacental placement at the time of cesarean section might confer an increased risk of expulsion compared with normal placement, the risk appears lower than that for placement at the time of vaginal delivery. Evidence for infection and perforation occurrence and removals for pain or bleeding are limited; however, these events are rare.[7]

Stuart et al.[56] conducted a RCT comparing the early placement (6–48 h) after vaginal delivery to the standard (at the standard postpartum visit) placement. The primary objective of the study was to compare the effects on breastfeeding prevalence, but the study was stopped prematurely due to the high rate of spontaneous expulsions in the early group. They found an even higher rate than that found in other studies conducted on insertion from 10 minutes to 72 h[57,58] and on postplacental insertion.[59,60] Stuart et al.[56] concluded that having a LNG-IUS placed 6 weeks after a vaginal delivery is superior to having a LNG-IUS placed between 6 and 48 h, due to the high rate of expulsion during early placement. They emphasized, however, that in special cases where it is very unlikely that the woman will return to the postpartum visit, and, after adequate counseling on the high rate of expulsion, early insertion may be considered.

A recent retrospective cohort study conducted by Ramos-Rivera et al.[61] demonstrated a higher uterine perforation rate with interval postpartum IUD placement at 4–8 weeks than at 9–36 weeks postpartum, with a difference in perforation rate of 0.32%. However, the uterine perforation rate was low overall (<1% in both groups). On the other hand, expulsion rates were not significantly different between insertion at 4–8 weeks (1.0%) and at 9–36 weeks (1.2%) postpartum. As reported by Stuart et al.,[56] Ramos-Rivera et al.[61] concluded that women, after proper counseling, should be offered IUD insertion at their desired postpartum time interval, given the significant positive public health impact of providing effective contraception soon after delivery.

Breastfeeding status seems to have the greatest impact on increasing the odds of uterine perforation.[61] More controversial, however, is the impact on the risk of expulsion. Breastfeeding is associated with short- and longer-term maternal endocrine and genitourinary changes after birth (to uterine morphology, peristalsis, the uterotonic effect of oxytocin, and pituitary-induced amenorrhea secondary to breastfeeding) and it may also be associated with expulsion of a IUD that has been immediately placed.[62–64] Although postpartum women with copper IUDs who were breastfeeding have been reported to experience similar or lower risks of expulsion relative to those who were not breastfeeding,[65] the association of breastfeeding with expulsion rates for other IUD types has not been extensively studied. Armstrong et al.[66] conducted a cohort study demonstrating that breastfeeding (vs. not) at IUD insertion was associated with an approximately 30% lower risk of its expulsion. Armstrong et al.[66] associated this reduction in risk with the protective effect of LAM.

The other open debate concerns the effect of the device itself on breastfeeding. One RCT found that immediate LNG-IUS insertion was associated with decreased breastfeeding duration compared with delayed insertion.[67] On the contrary, as shown above for

implants, two other RCTs assessing early versus delayed initiation of progestin-only contraceptives failed to show a difference in breastfeeding outcomes.[45,53] Also, the initiation of LNG-IUSs immediately postpartum had no other harmful effect on infant health, growth, or development.[39,68] In other studies, LNG-IUS initiation at 4 weeks postpartum or later demonstrated no detrimental effect on breastfeeding outcomes.[12,69,70]

In conclusion, according to the ACOG Committee on Obstetric Practice, "despite the higher expulsion rate of immediate postpartum IUD placement over interval placement, evidence from clinical trials and from cost-benefit analyses strongly suggest the superiority of immediate placement in reduction of unintended pregnancy, especially for those at greatest risk of not having recommended postpartum follow-up".[47] However, it has yet to be understood whether this approach can really have an advantage in high-income countries, where most women undergo a postpartum medical visit within 2 months of giving birth.

Although international official guidelines make no distinction between low- and high-income countries, it might be useful to put the contraceptive choice into the organizational context. In a context where the moment of delivery is often the only contact a woman has with medical facilities, an "immediate insertion" approach could bring real benefits to that woman's family planning perspective. On the contrary, in a context where women regularly visit within a few months after giving birth, this approach must be questioned. Although this is certainly true for IUS placement, where the rate of expulsion/malpositioning is clearly higher near delivery, it is absolutely not true for another long-acting reversible contraception methods, such as implants: for this contraceptive, the sooner it is placed the better!

6 | CONCLUSIONS

Different international guidelines generally agree about the possibility of different contraceptive methods used in the postpartum period, even if we have also highlighted substantial differences in the management of some situations, in relation to breastfeeding and the hypercoagulability state.

It is not clear whether the use of CHC in the immediate postpartum period can negatively affect breast milk or infant growth, whereas estrogen use certainly carries an increased thromboembolic risk for the mother. As a precaution, the initiation of CHC should be considered according to the most conservative guideline possible, taking into account other risk factors for thrombosis that the mother may present. However, the initiation of progestin-only methods (POP and implant) can be very early. In fact, according to the guidelines, there are no contraindications, in terms of thromboembolic risk, to start them immediately postpartum. Contraception using LNG-IUS and copper-IUD can also be started early, paying attention to the period between 48 h and 4 weeks postpartum and to puerperal sepsis risk. This manuscript is a narrative review of the leading recommendations of specialist societies and organizations in the area, but nothing is stronger than the treating physician's individualized decision making.

It is good to get to know guidelines thoroughly in order to be able to offer our women the best customized contraceptives, as early as possible but at the ideal timing.

AUTHOR CONTRIBUTIONS

Giovanni Grandi made a substantial contribution to the conception and design of the work, the draft and revised manuscripts, and final approval. Maria C. Del Savio made a substantial contribution to the design of the work, the draft manuscript, and final approval. Alice Tassi made a substantial contribution to the design of the work, the revised manuscript, and final approval. Fabio Facchinetti made a substantial contribution to the conception and design of the work, the draft and revised manuscripts, and final approval.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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