

# Insertion of intrauterine devices after cesarean section: a systematic review update

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**Background:** Women who undergo a cesarean section (CS) are in a unique position to receive the intrauterine contraceptive device (IUD). They may also want to use the IUD as a long-acting reversible contraceptive method provided the IUD is safe and effective in the presence of a CS scar.

**Search strategy:** We researched and reviewed the MEDLINE, POPLINE, Google Scholar, and [ClinicalTrials.gov](http://ClinicalTrials.gov) databases from January 1968 to June 2015.

**Selection criteria:** Eligible studies reported event rates or practical problems relating to IUD usage in post-placental or interval insertion (>90 days) after CS. Studies with  $\geq 20$  subjects were included.

**Data collection and analysis:** Analysis of eligible data collected from the search followed the PRISMA guidelines.

**Main results:** Twelve eligible studies of post-placental IUD insertion after CS included four randomized controlled trials of post-placental versus delayed insertion. Women randomized to delayed insertion were less likely to receive a device. Six studies examined the problem of missing IUD threads at follow-up with only 30%–60% presence of strings observed.

**Conclusion:** The IUD is a long-acting reversible contraceptive method that is suitable for use in all women undergoing CS. The problems of device expulsion, missing threads at follow-up, and the tendency of increased puerperal bleeding need to be solved. Solutions are proposed.

**Keywords:** post-placental IUD, cesarean section, missing IUD threads, IUD expulsion, long-acting reversible contraception

## Introduction

LARC is the most clinically and economically effective type of contraception.<sup>1,2</sup> Implants and IUDs have a rapid action of onset after administration with a rapid return to fertility after discontinuation.<sup>3,4</sup> LARC methods are therefore ideally suited to play a major role in fertility regulation worldwide as well as in Global South (GS) or impoverished countries.

CS rates are rising in all countries, including those of the GS.<sup>5</sup> IUD insertion at the time of CS creates an opportunity to increase access to LARC methods. Conversely, a previous CS scar may deter access to interval insertion of an IUD if a previous CS may result in difficulty with insertion and/or future IUD problems. We updated a previous systematic review<sup>6</sup> to see if post-placental and interval IUD insertion could be made more accessible for women wanting to use this method.

Even though it has only been a few years since our initial review, there have been a number of new detailed studies in this area.<sup>7–21</sup> The later, newer studies are constructed and some are controlled so that we are able to get a better understanding of how best to utilize the post-placental CS opportunity, and how to deal with the CS scar in those

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women who want an IUD after having previously had a CS. This review updates our previous analysis of insertion of IUDs in women who have had a CS and where IUD insertion has been post-placental or interval.

## Methods

This study is a systematic review to evaluate complications and performance after an IUD is inserted into women who have had a CS. There are two main categories: 1) insertion at the time of CS, ie, PPIUDCS and 2) interval insertion<sup>6</sup> (42 days or more after CS [IIUDCS]).

In more recent studies this distinction may have become slightly blurred since the newer studies have subjects in both groups ie, post-partum and very early interval, as they are controlled and compare post-placental insertion with 6- to 8-week post-partum insertion as a control group.<sup>12,13</sup> The control group thus “straddles” the boundary of post-partum and interval<sup>6</sup> insertion. We will consider these as interval insertions (IIUDCS) as opposed to post-placental insertions, since post-placental insertions are defined by being able to place the device in the uterine cavity under direct vision, the only time it is possible to do this. The straddled insertions at 6–12 weeks post-partum have been added to the to the IIUDCS group.

The methods used for data collection have been described in the previous study<sup>6</sup> and included both controlled and uncontrolled studies, but were modified as described in the following section. The reference list for this study was generated from searching for references from the following databases: MEDLINE: “Intrauterine device (IUD, IUCD)”/“Intrauterine system (IUS) [MeSH]” AND “Caesarean section, caesarean section CS, C/S [MeSH]”. “Intrauterine device (IUD, IUCD)”/“Intrauterine system (IUS)”. POPLINE: “IUD” AND “cesarean section”. PubMed: “IUD” AND “cesarean section”. Google Scholar: “IUD”, “IUS” AND “post-placental cesarean section”, AND “IUD” AND “interval cesarean section”, the terms were filtered so as not to overlap in the advanced search. [ClinicalTrials.gov](http://ClinicalTrials.gov): “intrauterine device” AND “cesarean section”. We did not search Wangfang Data and Weipu Data. Significant Chinese articles are beginning to appear in English language databases. Our study updates peer-reviewed papers from January 1968 to December 2012, which formed the basis of the previous report. In that study we searched for references from January 1968 to December 2012. The current search was divided into two parts: 1) to see if new references (especially foreign language) were added to the databases during that period (January 1968 to December 2012); and 2) to do an updated search from December 2012 to June 2015. This latter search is the main focus of this report.

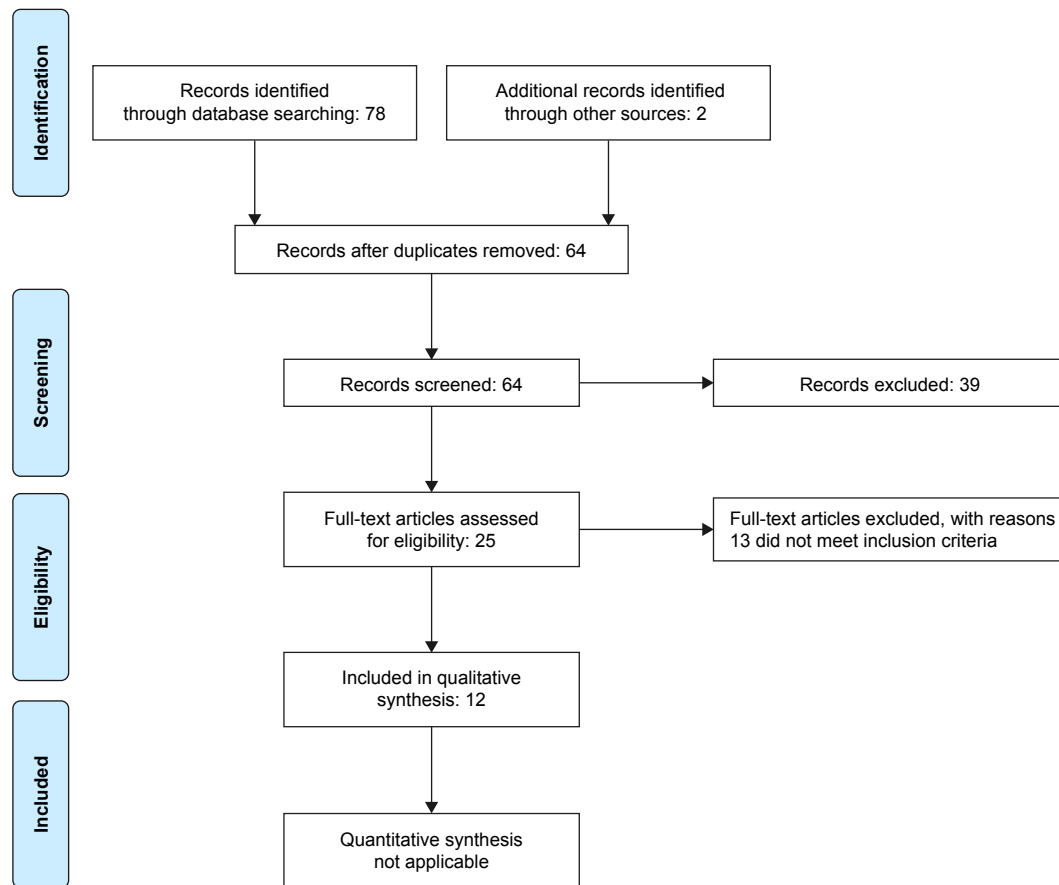
The inclusion criteria for selection of studies were broadened. Previously, we only included studies that contained principal event rates (pregnancy, expulsion, medical removal, and continuation rate) in at least 20 subjects. In this study we have included clinical complications such as pain, bleeding, discomfort, missing strings, and any other adverse reports in studies of  $\geq 20$  subjects. The systematic review section was conducted following the PRISMA guidelines,<sup>22</sup> a flow chart of selection of articles from January 2013 to June 2015 is given in Figure 1. We did not search the Chinese databases, but we actively searched for non-English articles that are increasingly being added to current databases, especially POPLINE. Higher weighting was given to RCTs and those with higher degrees of evidence, as indicated in the PRISMA guidelines.<sup>22</sup> These types of studies are now more common, as interest is growing in this area. We found two Chinese<sup>23,24</sup> and one Malaysian study<sup>25</sup> in the PPIUDCS group prior to December 2012, and one Chinese study in the IIUDCS group. The January 2013 to June 2015 search produced 12 papers in the PPIUDCS group, and two in the IIUDCS group. The selection process is given in Figure 1.

The previously missing references were found by repeating the POPLINE search, which found the new references that had been added by POPLINE to their database in the interim. These references have been added to our earlier database, and the table of post-partum CS insertion from our earlier paper has been updated (Table 1). Summary odds ratios were not computed because of the highly nonhomogeneous data reporting methods.

## Results

The search of the older references added a Lippes loop (Ortho, Raritan, NJ, USA) study in Malaysia,<sup>25</sup> a Chinese study of the GyneFix PP (Contrel Europe NV, Ghent, Belgium),<sup>23</sup> and an RCT of the Fix-T-Cu 220C-M and the Delta T-Cu220C to the PPIUDCS group. These have been added to the old database of experience (January 1968 to December 2012) and are presented in Table 1.<sup>26–39</sup> There was one IIUDCS study of the VCu200 IUD, which was a comparative study of subjects who had a CS versus those who had not had a CS at 42–90 days post-partum. This study has been added to the previous studies of mostly older IUDs.<sup>6</sup> In the VCu200 study, there was one ectopic pregnancy (0.32%) and at 2-year follow-up the expulsion rate was 2.68 per 100 woman years of use for the CS group, and 2.65 for the non-CS group. The pregnancy rate for the CS group was 4.49, and 5.88 for the non-CS group per 100 woman years of use, as determined by life table analysis. The tendency,

## Selection of relevant articles for intrauterine device insertion after cesarean section



**Figure 1** Flow chart of selection of articles from December 2012 to June 2015 (PRISMA).

**Abbreviation:** PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

since the end period of the last review (from 2013 onwards), has been a move to controlled studies of different IUDs with different time periods in the PPIUDCS groups. It is this information which can provide the “which” and the

“when” for PPIUDCS and IIUDCS insertion, and can help improve clinical practice.

Ten studies from the January 2013 to June 2015 search met the criteria for inclusion in the PPIUDCS group, the

**Table 1** Updated PPIUDCS studies published before December 2012

Event rate per 100 woman years (range)						
Type of IUD	Studies	Subjects followed	Expulsion	Medical removal	Pregnancy	Comments and references
Mirena	1	33	0	0	0	12-month follow-up <sup>27</sup>
MLCu 250	1	154	2.6%	7.8%	0	12-month percentage rate <sup>28</sup>
TCu220	3	714	(1.78–10.9)	Not stated	0–1.1	12-month cumulative rate <sup>29–31</sup>
TCu380A	5	314	(0–17.6)	(0–10.6)	0	One study had 6-month follow-up <sup>32–36</sup>
Delta T	2	135	(4.1–9.6)	7.2	2.4	One reported 6-month cumulative, the other 24-month percentage rates <sup>37,38</sup>
Delta loop						
Delta Beijing						
GyneFix PP IUD <sup>a</sup>	1	200	4%	Not stated	0	3-month percentage rates <sup>23</sup>
Fix-T-Cu 220C-M <sup>a</sup>	1	200	2.2%	2.5%	0.5%	RCT at 30 months. 30-month cumulative life table rates <sup>24</sup>
Delta-TCu 220C <sup>a</sup>		200	10.5%	2.6%	0.5%	Cumulative rate from 6–24 months <sup>38,39</sup>
Metal ring-catgut knots	7	3,131	(1.2–9.6)	(0.8–7.2)	(0–7.5)	Cumulative rate from 6–24 months <sup>38,39</sup>
Lippes loop <sup>a</sup>	1	204	12.2%	3.9%	0.49%	12-month percentage rates <sup>25</sup>

**Notes:** <sup>a</sup>Newly added studies. Chi et al<sup>38</sup> reported nine Chinese studies that were also reported in Chi et al<sup>37</sup> and Liu et al.<sup>39</sup> The data were only used once. Mirena (Bayer AG, Levekusen, Germany); MLCU 250 (Multilan SA, Fribourg, Switzerland); TCu220 (Population Council, New York, NY, USA); TCu380A (Teva Pharmaceuticals, Petach Tikva, Israel); (Delta T, Delta loop, Delta Beijing, [Chinese government, Beijing, People’s Republic of China]); Lippes loop (Ortho, Raritan, NJ, USA); GyneFix PP (Contrel Europe NV, Ghent, Belgium); (Fix-T-Cu 220C-M, Delta-TCu 220C, [Chinese Government, Beijing, People’s Republic of China]).

**Abbreviations:** PPIUDCS, post-placental IUD at CS; CS, cesarean section; IUD, intrauterine contraceptive device; RCT, randomized controlled trial.

selection process is shown in Figure 1. Two studies met the inclusion criteria in the IIUDCS group.<sup>8,16</sup> These two studies, which examined the use of interval IUD insertion in women who had had a previous CS, were designed to examine insertion problems rather than event rates. The first study<sup>8</sup> evaluated pain during insertion of the LNG releasing IUD (LNG IUD) in 28 parous women who had undergone at least one CS compared with 23 nulligravid women and 23 parous women who had not undergone CS. Nulligravid women experienced the most pain, followed by women with previous CS. The second study evaluated the use of misoprostol versus diclofenac before IUD insertion in women who had only given birth by CS. One hundred and thirty women were given misoprostol 400 µg sublingually and 100 mg diclofenac orally, while 125 were given diclofenac orally only.<sup>16</sup> The use of misoprostol in addition to diclofenac did not help with the insertion process. Ease of insertion and pain experienced with the insertion was the same in both groups. Insertion failure rates were similar in both groups. The misoprostol group experienced more abdominal pain and nausea. There were no new studies on expulsion rates in IIUDCS insertions. Our previous data, showing a greater incidence of expulsion with older and much older devices in interval insertion in women with previous CS,<sup>6</sup> cannot be updated for TCu380A (Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel), LNG IUD, Nova T 380 (Bayer AG, Levekusen, Germany), and GyneFix PP, which are the IUDs in current use.

There were therefore a total of 12 new eligible papers from December 2012 to the present day search<sup>7-17,19-21</sup> (10 PPIUDCS and 2 IIUDCS). Our expanded inclusion criteria also allowed us to include two papers from the earlier search that did not meet the previous inclusion criteria.<sup>7,10</sup> Both were studies that focused on puerperal bleeding, which is of particular relevance in low socioeconomic environments. These two studies have been added to the ten (PPIUDCS) from the later search and are presented in Table 2. There was one RCT of three different devices, Nova T 380, TCu380A, and MLCu 375 (Multiload Copper375; Multilan SA, Fribourg, Switzerland), with significantly lower expulsion rates for the MLCu 375.<sup>14</sup> This RCT is the first three-way study that attempts to evaluate which type of IUD is superior, and not assume they behave generically in this situation unless they are tethered to the uterine fundus.<sup>20</sup> There were four RCTs of PPIUDCS insertion versus interval insertion (at 4–8 weeks).<sup>12,13,15,17</sup> All had small numbers and limited follow-up. They all showed that those allocated to the delayed insertion group very often failed to present for their later insertion. This was true in both developed countries like Australia,<sup>13</sup> and GS countries like

Uganda.<sup>12</sup> One study described a new technique to anchor the IUD to the fundus (hang up) to prevent expulsion,<sup>20</sup> while one examined elongating threads to help prevent the problem of missing threads.<sup>14</sup> Expulsion rates were very variable, with no expulsions in studies with very small numbers<sup>13,17</sup> and where the device was sutured into the uterus,<sup>20</sup> while in other studies it varied between 10% and 15%. There were no reports of perforations.

While expulsion and missing strings are important problems everywhere, they are of particular significance for situations in which ultrasound is not available, which is often the case in the GS. Two studies examined the effect of IUD type on puerperal bleeding.<sup>7,10</sup> LNG IUD was significantly better in reducing puerperal blood loss which is important in helping to prevent anemia, and this is of major importance in areas where undernourishment may be prevalent, as is often the case in the GS.

We have analyzed reports of missing strings from those studies in which it has been detailed. The information that is available is presented in Table 3 and its importance is discussed later. Elongating the threads and guiding them through the cervix results in strings being visible in all cases.<sup>14,36</sup> For IUDs that have long threads eg, ML Cu375, simply pushing the threads through the cervix at the time of CS produces a 92% visibility rate at 6 weeks and 6 months.<sup>7</sup> If the threads of the TCu380A are left at the incision length, then follow-up visibility is around 30%–40%. The same is true for the LNG IUD, where string visibility of 30%–60% was reported in two studies.<sup>13,15</sup> The elongated strings require trimming at follow-up. Missing strings require that the presence and position of the IUD be verified by ultrasound, which as previously stated, is a big problem for clinics in GS countries. There were 70 LNG IUDs placed at 6 weeks post-partum after CS in three studies<sup>13,15,17</sup> and 22 TCu380A IUDs.<sup>12,15</sup> At 6-month follow-up there were seven LNG IUD expulsions and one expulsion in the TCu380A group. Losses to follow-up of around 14% were analyzed using the “intention to treat” method.

## Discussion

The first study on the use of PPIUDCS was by Zervy in 1967.<sup>40</sup> He inserted a Birnberg Bow size 5 or 7 and sutured it in place at CS. After that there were relatively few studies over many years. The main reason for this is that IUDs were firmly in the shadow of the infection scare. The risks of the procedure appeared to override the potential benefits. Sporadic attempts to revive the procedure were made in the 1970s and 1980s. This anxiety regarding PPIUDCS began

Table 2 PPIUDCS

Author (year)	Study design and IUD	Population	Comparison	Event rates		Comments	
				Expulsion	Medical removal	Pregnancy	
Bhutta et al <sup>8,7</sup> (2011)	MLCu 375 insertion at CS vs 6 W and no IUD	PPIUDCS 50 IIUDCS 50 Control 50	Post-placental vs 6W vs no IUD	Same in all groups	Same in all groups	0	6 M follow-up. No difference in puerperal bleeding in all groups
Elsedeek <sup>10</sup> (2012)	Nova T 380 vs Mirena vs control at CS	Nova T 380 63 Mirena 60 Control 63	Nova T vs Mirena on puerperal bleeding	No numbers given Nova T 7.9% Mirena 0%	No numbers given 0 0	0	Nonrandom. 6 W follow-up. Mirena group bled significantly less
López-Farfán et al <sup>9</sup> (2012)	Mirena vs TCu380A at CS. RCT	Mirena 198 TCu380A 198	Mirena vs TCu380A	Mirena 4.5% TCu380A 4.5%	2% 3.5%	0	12 M percentage rates
Gueye et al <sup>19</sup> (2013)	Open evaluation of TCu380A at CS. Uncontrolled	PPIUDCS 56	0	2.2%	2.3%	0	6 M percentage follow-up rates
Singal et al <sup>21</sup> (2014)	Open evaluation of TCu380A at CS	PPIUDCS 300	0	5.23%	7%	0.6%	12 M percentage rates
Tjahjantto et al <sup>20</sup> (2014)	Open evaluation of TCu380A sutured to fundus at CS - "hang-up" technique	PPIUDCS 108	0	0	0.95%	0.9%	Pearl index and percentage rates at 12 M
Whitaker et al <sup>17</sup> (2014)	Mirena at CS vs at 4-8 W post-CS. RCT	PPIUDCS 20 IIUDCS 22	Mirena at CS vs later insertion at post-partum visit	At CS 20% At 4-8 W 0%	Not stated	0	12 M follow-up. Percentage rates
Braniff et al <sup>13</sup> (2015)	Mirena at CS vs 6 W post-CS. RCT	PPIUDCS 23 IIUDCS 19	Mirena at CS vs later insertion at post-partum visit	At CS 0% At 6 W 0%	Not stated	0	6 M follow-up. Percentage rates. High satisfaction in both groups
Lester et al <sup>12</sup> (2015)	TCu380A at CS vs 6 W post-CS. RCT	PPIUDCS 34 IIUDCS 18	TCu380A at CS vs later insertion at post-partum visit	At CS 3% At 6 W 5%	At CS 3% At 6 W 5%	0	6 M follow-up. Percentage rates
Levi et al <sup>15</sup> (2015)	Comparison of Mirena and TCu380A at CS vs 6 W+ post-CS. RCT as to timing of insertion	Mirena PPIUDCS 40 TCu380A PPIUDCS 15 Mirena IIUDCS 30 TCu380A IIUDCS 4	Mirena or TCu380A at CS vs later insertion at post-partum visit	At CS (combined results) 8% At 6 W (combined results) 2%	At CS (combined results) 15% At 6 W (combined results) 4%	0	6 M follow-up. Percentage rates. Participants selected type of IUD
Elsedeek <sup>11</sup> (2015)	Mirena vs Nova T 380 at CS. Open study	Mirena 80 Nova T 63	Mirena vs Nova T at patient request	Mirena 0% Nova T 6.3%	Mirena 3.8% Nova T 7.9%	Nova T 6.3% Mirena 0%	60 M follow-up. Percentage rates, misalignment at 6 W more common with Mirena
Ragab et al <sup>14</sup> (2015)	Nova T 380 vs TCu380A vs MLCu 375 at CS. RCT	Nova T 380 40 TCu380A 40 MLCu 375 40	Three-way comparison of different copper IUDs inserted at CS	Nova T 13% TCu380 15% MLCu 5.6%	Not stated	Nova T 3% TCu380 3% MLCu 0%	12 M follow-up. Percentage rates. Expulsion rate of MLCu 375 was significantly lower than the other two Springs lengthened with vicary

**Notes:** Results from December 2012 to June 2015 search, unless otherwise stated. <sup>a</sup>Included from earlier search because of widened inclusion criteria. Mirena (Bayer AG, Leverkusen, Germany); Nova T 380 (Bayer AG); MLCu 375 (Multiload Copper 375; Multilan SA, Fribourg, Switzerland); TCu380A, Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel).

**Abbreviations:** PPIUDCS, post-placental IUD at CS; IIUDCS, interval insertion of IUD after CS; CS, cesarean section; IUD, intrauterine contraceptive device; RCT, randomized controlled trial; vs, versus; W, weeks; M, months.

**Table 3** Missing strings after PPIUDCS

Study	IUD	Number	Strings observed (%)	Interval after insertion	Comments
Zhang H et al <sup>23</sup>	GyneFix PP	200	86	6 W	The device is attached to the fundus under direct vision
Nelson et al <sup>36</sup>	TCu380A	7	100	6 W	Modified extended strings guided through cervix into vagina
Levi et al <sup>34</sup>	TCu380A	32	28	6 W	Normal strings placed in the cervix
Lester et al <sup>12</sup>	TCu380A	27	44	6 W	
Bhutta et al <sup>7</sup>	MLCu 375	50	92 and 92	6 W and 6 M	Long thread of MLCu 375 pushed through the cervix
Singal et al <sup>21</sup>	TCu380A	300	61 and 84	6 W and 12 M	More strings seen at 12 M follow-up
Braniff et al <sup>13</sup>	Mirena	23	31.6	6 W	Strings not directed through the cervix
Levi et al <sup>15</sup>	Mirena	21	67	6 M	
	TCu380A	10	40	6 M	
Ragab et al <sup>14</sup>	Nova T 380	40	100	6 W and 60 W	Strings lengthened with vicryl and placed through cervix into the vagina
	MLCu 375	40	100		
	TCu380A	40	100		

**Notes:** Mirena (Bayer AG, Levekusen, Germany); Nova T 380 (Bayer AG); MLCu 375 (Multiload Copper375; Multilan SA, Fribourg, Switzerland); GyneFix PP (Contrel Europe NV, Ghent, Belgium).

**Abbreviations:** PPIUDCS, post-placental IUD at CS; IIUDCS, interval insertion of IUD after CS; CS, cesarean section; IUD, intrauterine contraceptive device; W, weeks; M, months.

to dissipate in the 1990s due to the realization that the IUD is not primarily responsible for causing infection<sup>41</sup> and the introduction of the LNG IUD/IUS (Mirena). More recently there has been renewed interest in LARC, because of its well described role in limiting unintended pregnancies.<sup>1</sup> Inserting an IUD at the time of CS is a very attractive option. It adds very little time and cost to the procedure. The patient does not have to come back especially for follow-up, and there is no risk of primary perforation (secondary perforation is possible) as it is performed under direct vision. Should it remain in place a 5-year follow-up seems to indicate that it will behave similarly to interval insertion in woman with and without CS.<sup>14</sup>

There appears to be two early problems with PPIUDCS. Initial expulsion rates, although not as high as those after vaginal birth post-partum insertion, are still unacceptably high (5%–10%). This is the only time an IUD is inserted into the uterine cavity under direct vision, and the use of the correct anchor has the ability to make the expulsion rate close to zero.<sup>20,42,43</sup> If a method to hold the IUD in the uterus is used, eg, with suturing into the uterine muscle techniques,<sup>20</sup> expulsion can be reduced to below 1%. This adds to the complexity of the procedure, and in most cases requires additional training for those inserting the devices. The second problem of importance is missing threads. In many GS situations ultrasound is often not available, making this a time-consuming problem which often mandates referral to a tertiary center. Techniques for lengthening threads to ensure their presence in the vagina exist, but often necessitate trimming and so may require an extra post-partum follow-up. However, this is easier to undertake than referral for ultrasound, and

post-partum evaluation should be conducted anyway, but even this can create difficulties in the GS.<sup>14,36</sup> The problem of missing strings after PPIUDCS insertion is of considerable importance with regard to advancing this method in the GS. There have been various approaches to attempt to resolve this problem. In one study vicryl was used to lengthen the threads.<sup>14</sup> The use of absorbable material which ensures that the strings remain visible, but subsequently absorb so that they are not too long, may be a solution. These techniques are among those which have the capacity to expand access in the GS and indeed worldwide.

The use of 6-week controls has created a new group of post-CS IUD recipients for study. While the insertion of IUDs at the 6-week follow-up after CS is not new, we added the results of insertions at 42–90 days post-CS<sup>26</sup> and the 6-week post-CS insertions in the newer studies. The difference between the post-CS at around 6 weeks and the truly interval insertions ( $\geq 90$  days post-CS) is the risk of certain specialized complications, eg, perforations.<sup>44</sup> For this reason we consider that this group should be examined separately from PPIUDCS and IIUDCS. There is as yet no study reporting the outcomes of insertions performed exclusively in the 40–45 days post-CS period.

## Conclusion

PPIUDCS has many practical advantages. The recipient can leave with the IUD in place and will be protected from pregnancy even if she does not attend follow-up, provided the IUD remains in place. Further evidence from systematic review of recent studies is providing us with new information to help make this a more acceptable option for women

in the GS and elsewhere. In order to expand access to this procedure there are three main problems to be solved, namely: 1) prevent expulsion – whether by device design or suture technique; 2) ensure that strings are visible, and if possible do not require adjustment; and 3) reduce puerperal bleeding – hopefully by the use of cheaper hormone releasing devices, which should soon become available.

## List of abbreviations

CS, cesarean section; IUD, intrauterine contraceptive device; LARC, long-acting reversible contraceptive; GS, global south; PPIUDCS, post-placental IUD at CS; RCT, randomized controlled trial; IIUDCS, interval insertion of IUD after CS; LNG, levonorgestrel.

## Disclosure

The authors report no conflicts of interest in this work.

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