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Updates on Using Prostaglandins for the Management of Retained Placenta: A Systematic Review

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ABSTRACT

Objectives: To review the current evidence on the management strategies using prostaglandin analogues for the retained placenta (RP). Methods: A comprehensive exploration of relevant databases was conducted to identify studies meeting the inclusion criteria. To locate relevant literature, a comprehensive search of PubMed, Web of Science, SCOPUS, and Science Direct was carried out. The entire procedure made use of the Rayyan QRCI. Results: Fifteen trials including 2604 women with retained placenta were included in our data. Only two studies documented that there was no difference between the effectiveness of prostaglandin and other comparators; sulprostone and 400 µg misoprostol. Six studies stated that prostaglandins, mainly misoprostol, MPR more effective than the comparator groups in decreasing blood loss and requirement for manual placenta removal. Rectal administration of prostaglandin analogues was effective in decreasing postpartum hemorrhage. The prostaglandin administration sublingually, orally, and vaginally was not effective in decreasing MRP or blood loss. Conclusion: In comparison with, oxytocin, oxytocin agonists, ergometrine, and placebo the use of prostaglandins through intraumbilical vein injection and rectally was superior and showed better results in managing retained placenta. To select which prostaglandin to use and at what dose for the medical management of retained placenta, more research is required.

KEYWORDS: Retained placenta, Maternal complications, Systematic review, Management strategies.

1. Introduction

Retained placenta is a common complication that occurs in approximately 3-4% of all vaginal deliveries. It is defined as the failure of the placenta to be expelled within 30 minutes after the delivery of the baby. This can lead to significant maternal morbidity and mortality if not managed promptly and effectively [1].

In recent years, there have been significant updates in the types and management of retained placenta. One of the key advancements is the classification of retained

placenta into three main types: adherent, increta, and percreta [2]. Adherent placenta occurs when the placenta is firmly attached to the uterine wall, increta when it invades the myometrium, and percreta when it penetrates through the uterine wall and may even invade adjacent organs. This classification helps in determining the appropriate management strategy for each type of retained placenta [2].

The management of retained placenta has also evolved with the introduction of new techniques and technologies. One of the most common methods used to manage retained placenta is manual removal under anesthesia. However, this can be associated with significant risks such as hemorrhage and infection [3]. As a result, there has been a shift towards more conservative management strategies, such as the use of intrauterine tamponade devices, uterine artery embolization, and even the use of medications like misoprostol to help facilitate placental expulsion [4].

In cases where conservative management fails, surgical interventions such as dilation and curettage or even hysterectomy may be necessary to remove the retained placenta. However, these procedures are associated with increased risks and should only be considered as a last resort [5].

Overall, the updates in types and management of retained placenta have provided healthcare providers with a better understanding of this complication and have improved outcomes for women experiencing this condition. It is important for healthcare providers to stay informed about these updates and to be prepared to manage the retained placenta effectively to ensure the best possible outcomes for both mother and baby [6, 7].

The study aims to address the current gaps in knowledge regarding the types and management of retained placenta. By conducting a systematic review, the study seeks to provide an updated and comprehensive overview of the available literature on this topic. Retained placenta is a common obstetric complication that can lead to serious maternal morbidity and mortality if not managed promptly and effectively. Despite advancements in medical technology and interventions, there is still a lack of consensus on the optimal types and management strategies for retained placenta. This study aims to identify the key issues and challenges in this area.

The aim of this study is to conduct a systematic review of the literature to provide an updated understanding of the types and management of retained placenta. By synthesizing the available evidence, the study aims to contribute to the existing knowledge base and inform clinical practice in this area.

Study Objectives:

- To review the current evidence on the management strategies for retained placenta.
- To evaluate the outcomes associated with various management approaches.
- To identify gaps in the literature and areas for future research in the field of retained placenta management.

2. Methods

For our study, we followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8]. We conducted an electronic search of databases such as PubMed, Web of Science, SCOPUS, and Science Direct to identify relevant English-language studies on retained placenta. The search strategy included keywords related to the types and management of retained placenta. Two reviewers independently screened the search results, selected pertinent studies, extracted data, and assessed the quality of the included research using appropriate tools.

Eligibility Criteria:

Inclusion Criteria:

1. Studies published in the English language.
2. Studies focusing on the types and management of retained placenta.
3. Studies that provide clear definitions and classifications of retained placenta.
4. Studies that report on outcomes of different management strategies for retained placenta.
5. Randomized controlled trials, cohort studies, and case-control studies.
6. Studies published within the last 10 years to ensure relevance.

Exclusion Criteria:

1. Studies not published in the English language.
2. Studies not related to retained placenta.
3. Studies that do not provide clear definitions or classifications of retained placenta.
4. Case reports or case series with small sample sizes.
5. Studies with incomplete or insufficient data on management strategies for retained placenta.
6. Animal studies, editorials, commentaries, and conference abstracts.

Data Extraction

In our study, the accuracy of the search results was confirmed using Rayyan (QCRI) [9]. Titles and abstracts identified in the search were assessed for relevance based on the inclusion and exclusion criteria. Papers that met the inclusion criteria were subjected to a thorough review by the research team. Any discrepancies were resolved through agreement. Essential study details such as titles, authors, publication year, study location, participant characteristics, gestational age (GA), Intervention, route of administration of prostaglandin, findings, and conclusion were documented using a predefined data extraction form. An independent assessment tool will be devised to evaluate the risk of bias in the included studies.

Data Synthesis Strategy

In order to provide a qualitative evaluation of the research findings and components, summary tables were generated using data extracted from relevant studies. Once the data collection for the systematic review was complete, the optimal approach for utilizing the data from the included studies was determined.

Risk of Bias Assessment

The Joanna Briggs Institute (JBI) [10] critical assessment criteria for studies reporting prevalence data were applied in order to evaluate the study's quality. There are nine questions in this tool. replies that are negative, ambiguous, or irrelevant are scored zero, whereas replies that are positive are scored one. Less than four, five to seven, and more than eight ratings will be divided into three categories: low, moderate, and exceptional quality, respectively. Academics assessed the work's quality independently, and differences were resolved through debate.

The Cochrane Collaboration Risk of Bias (ROB) tool [11] was used to assess the risk of bias in the included randomized control trials. The results are shown in a table with different color schemes. Red denotes a large bias risk, green denotes a low risk, and yellow denotes an inability to determine the risk due to insufficient information.

3. Results

Search results

After 466 duplicates were removed, a total of 819 study papers were found through a systematic search. After 353 studies had their titles and abstracts evaluated, 301 papers were discarded. Merely two studies were not located out of the 52 reports that were required to be retrieved. 50 papers were screened for full-text assessment; 19 were rejected because the study results were wrong, 10 because the population type was inaccurate, 4 were letters to the editor, and 2 were abstracts. Fifteen research publications in this systematic review satisfied the requirements for eligibility. An overview of the procedure used to choose the research is illustrated in Figure 1.

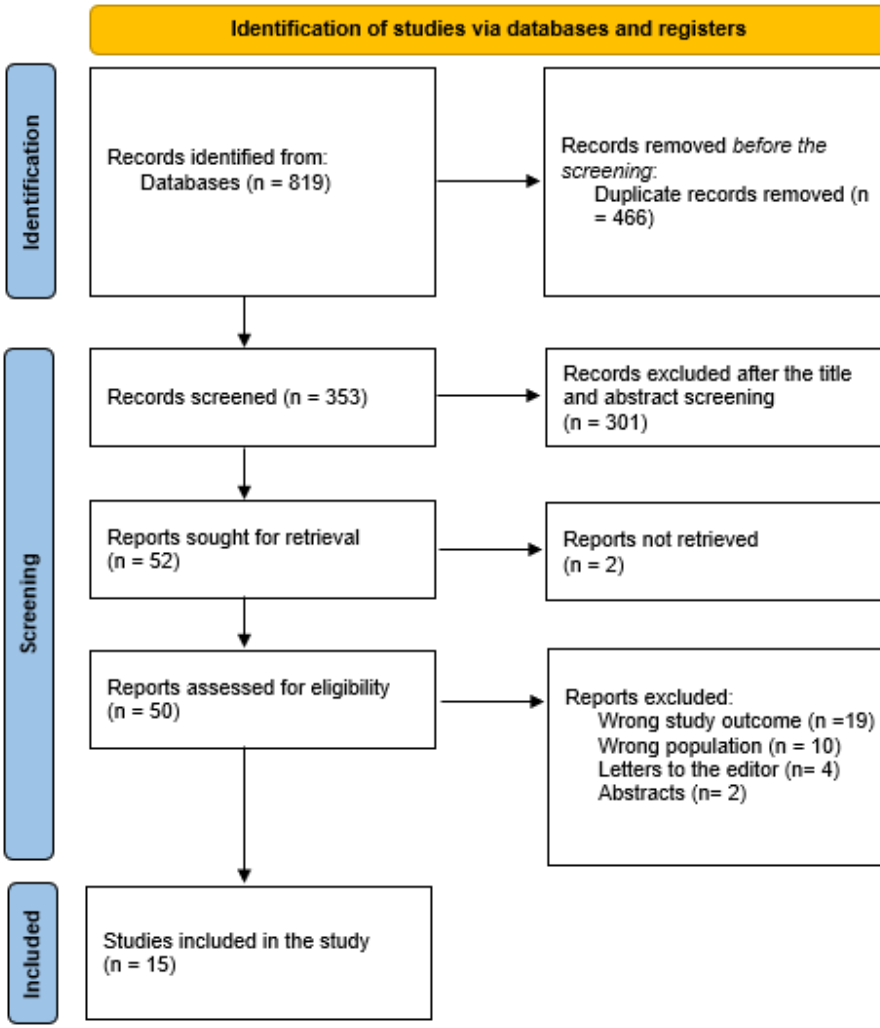

Figure (1): Study decision is summed up in a PRISMA diagram.

Sociodemographic features of the comprised studies

The research publications' sociodemographic information is displayed in Table 1. Fifteen trials including 2604 women with retained placentawere included in our data. Nine studies were randomized control trials (RCTs) [13, 15, 17-22, 25], four were retrospective cohorts [12, 23, 24, 26], one was a prospective cohort [14], and one was a case-control [16]. Three studies were conducted in Egypt [13, 15, 21], two in the Netherlands [12, 25], two in the USA [24, 26], one in Croatia [14], India [16], Iraq [17], Iraq [18], Iran [19], Pakistan [20], Tanzania [20], Nigeria [22], and Thailand [23]. The earliest studies were conducted in 2009 [14, 24] and the latest in 2023 [26].

Clinical outcomes according to the route of administration of prostaglandins Table (2)

Intraumbilical vein injection

Eight studies discussed the effectiveness of prostaglandin via intraumbilical vein injection in managing retained placenta. Only two studies documented that there was no difference between the effectiveness of prostaglandin and other comparators; sulprostone [12] and 400 µg misoprostol [15]. Six studies stated that prostaglandins, mainly misoprostol, MPR more effective than the comparator groups in decreasing blood loss [16, 17, 18] and the requirement for manual placenta removal [16, 19].

Sublingual administration

The two studies that discussed the prostaglandin administration sublingually were not effective in decreasing MRP or blood loss [20, 21].

Rectal administration

Rectal administration of prostaglandin analogues (misoprostol) was effective in decreasing postpartum hemorrhage [22, 23, 24].

Others

oral misoprostol administration does not appear to lower the number of MPRs [25]. Vaginal misoprostol in women with retained placenta had a lower success rate when using misoprostol to treat early pregnancy loss [26].

Risk of bias

Six studies were non-randomized studies and were assessed using the JBI tool [12, 24, 16, 23, 24, 26]; all were at moderate risk of bias. Nine studies were RCTs and we evaluated them using Cochrane presented in Figures (2 & 3) [13, 15, 17-22, 25].

Table (1): The sociodemographic attributes of the participating populations.

Study	Study design	Country	Participants	Mean age
Notten et al. 2014 [12]	Retrospective cohort	The Netherlands	Medical intervention group (N = 219) and Expectant management group (N = 275)	30.9 ± 5.3
Harara et al. 2011 [13]	RCT	Egypt	Oxytocin (n = 26), ergometrine (n = 27), and misoprostol (n = 25)	18-35
Habek et al. 2009 [14]	Prospective cohort	Croatia	Oxytocin (n= 54), carboprost tromethamine (n= 7), and methylergometrine (n= 14)	24.1 ± 7.6
Alalaf et al. 2020 [15]	RCT	Egypt	400 µg misoprostol (n = 274) and 800 µg misoprostol (n = 249)	28.8 ± 6.7
Patra et al. 2017 [16]	Case-control	India	Misoprostol (n=50) and Normal saline (n=50)	22.8 ± 4.5
Rajab & Alalaf 2014 [17]	RCT	Iraq	Misoprostol (n=23) and Normal saline (n=23)	24.5 ± 5.2
Najafian et al. 2018 [18]	RCT	Iran	Misoprostol (n=22) and Oxytocin (n=22)	30 ± 5
Nazeer et al. 2016 [19]	RCT	Pakistan	Misoprostol (n=30) and Oxytocin	22.4 ± 3.6

			(n=30)	
van Beekhuizen et al. 2013 [20]	RCT	Tanzania	Misoprostol (n = 65) and Placebo (n = 30)	27 ± 6.7
Maher et al. 2017 [21]	RCT	Egypt	Oxytocin group (n=96), Carbetocin group (n=94), and Misoprostol group (n=91)	27.8 ± 5.2
Akpan et al. 2021 [22]	RCT	Nigeria	Misoprostol (n = 74) and Placebo (n = 75)	20-49
Pongsatha & Tongsong, 2011 [23]	Retrospective cohort	Thailand	20	31.9 ± 6.3
Sundaram et al. 2009 [24]	Retrospective cohort	USA	RM (n = 161) and 15-methyl PGF2 (n = 142)	29.8 ± 4.5
van Stralen et al. 2013 [25]	RCT	The Netherlands	Misoprostol group (n = 48) and Placebo group (n = 51)	20-41
Cohen et al. 2023 [26]	Retrospective cohort	USA	237	32.6 ± 6.5

Table (2): Clinical features and results of the included research.

Study	GA	Intervention	Mode of administration of PGs	Findings	Conclusion	JBI
Notten et al. 2014 [12]	38.4 ± 3.02	800 µg of misoprostol versus 250 µg of sulprostone	Intraumbilical vein injection	Administering intravenous sulprostone and misoprostol via intraumbilical vein injection in succession does not lessen the overall volume of blood lost or the number of MRP in women with retained placenta.	No difference	Moderate
Harara et al. 2011 [13]	26-42	20 IU oxytocin, 0.2 mg ergometrine, and 800 mg misoprostol	Intraumbilical vein injection	Misoprostol is marginally more successful than oxytocin, ergometrine, and dissolved misoprostol in saline when it comes to managing retained placenta.	Favours misoprostol	NA**
Habek et al. 2009 [14]	35-41	20 IU oxytocin, 0.5 mg carboprost tromethamine, and 0.2 mg methylergometrine	Intraumbilical vein injection	76.9% of the oxytocin group, 85.7% of the synthetic prostaglandin group, and 64.2% of the methylergometrine group saw therapeutic success.	Favours prostaglandin	Moderate
Alalaf et al. 2020 [15]	28	400 versus 800 µg of misoprostol	Intraumbilical vein injection	Both 400 and 800 µg of misoprostol intraumbilical injections were safe and efficient ways to deliver retained placenta.	No difference	NA
Patra et al. 2017 [16]	39.2 ± 0.94	800 mcg of misoprostol versus 25 mL of normal saline	Intraumbilical vein injection	The requirement for manual placenta removal is much reduced when intraumbilical misoprostol is used. In the misoprostol group, there was less	Favours misoprostol	Moderate

				blood loss.		
Rajab & Alalaf 2014 [17]	37.22 ± 2.9	800 mcg misoprostol versus 20 mL of normal saline	Intraumbilical vein injection	Misoprostol injected into the umbilical vein is a useful treatment for retained placenta. It also minimizes vaginal blood loss with minimal side effects.	Favours misoprostol	NA
Najafian et al. 2018 [18]	35± 5	800 µg of misoprostol versus 50 units of oxytocin	Intraumbilical vein injection	Compared to umbilical vein injection of oxytocin, umbilical vein injection of misoprostol is more effective in managing elongated third-stage labor (retained placenta for more than 30 minutes) and also in reducing bleeding, particularly in instances without a history of vaginal trauma.	Favours misoprostol	NA
Nazeer et al. 2016 [19]	39.02 ± 1.10	800 mcg misoprostol versus 50 units oxytocin	Intraumbilical vein injection	When misoprostol is given intraumbilically instead of oxytocin via a comparable route, the requirement for manual placenta removal during general anesthesia is greatly reduced.	Favours misoprostol	NA
van Beekhuizen et al. 2013 [20]	28	Sublingual misoprostol (800 µg) versus placebo	Sublingually	Two-thirds of placentas held at 30 minutes spontaneously discharged within an hour of the neonate's delivery, with or without misoprostol medication. Neither MRP nor postpartum hemorrhage were reduced by misoprostol.	No difference	NA
Maher et al. 2017 [21]	NM	30 IU intraumbilical oxytocin, 1 ampoule carbetocin, and 400 µg misoprostol	Sublingually	For the oxytocin, carbetocin, and misoprostol groups, the overall success rates were 66.7% (64/96), 71.3% (67/94), and 63.7% (58/91), respectively (P > 0.05). Even though the goal was to favor one drug over another, they all appeared to be quite effective.	No difference	NA
Akpan et al. 2021 [22]	NM	400 ug of misoprostol versus placebo	Rectally	While both groups' overall postpartum hemorrhage incidence (0.070) was similar, the misoprostol group's incidence of severe PPH was lower than that of the placebo group (p = 0.013).	Favours misoprostol	NA
Pongsatha &	19-42	800 mcg	Rectally	When it comes to	Favours	Moderate

Tongsong, 2011 [23]		misoprostol		placental separation in situations of retained placenta, 800 mcg of rectal misoprostol is not as successful as anticipated.	misoprostol	
Sundaram et al. 2009 [24]	19.6 ± 2.8	800 µg misoprostol or 250 µg PGF2α	Rectally and intamuscularly	When PGF2α is used instead of rectal misoprostol following second-trimester deliveries, the third stage of labor is shorter and the rate of retained placenta is lower.	Favours PGF2α	Moderate
van Stralen et al. 2013 [25]	34-42	800 µg of misoprostol versus placebo	Orally	An hour after labor, 800 µg of oral misoprostol administration does not appear to lower the number of MPR.	No difference	NA
Cohen et al. 2023 [26]	NM	800 µg misoprostol versus controls	Vaginally	Women who experienced a retained placentahad a lower success rate when using misoprostol to treat early pregnancy loss.	Not effective	Moderate

*NM=Not-mentioned

*NA=Not-applicable

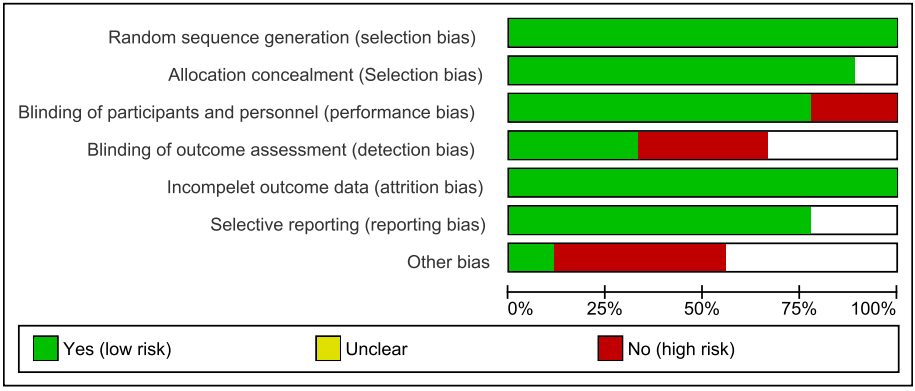

Figure 2: Bias risk graph.

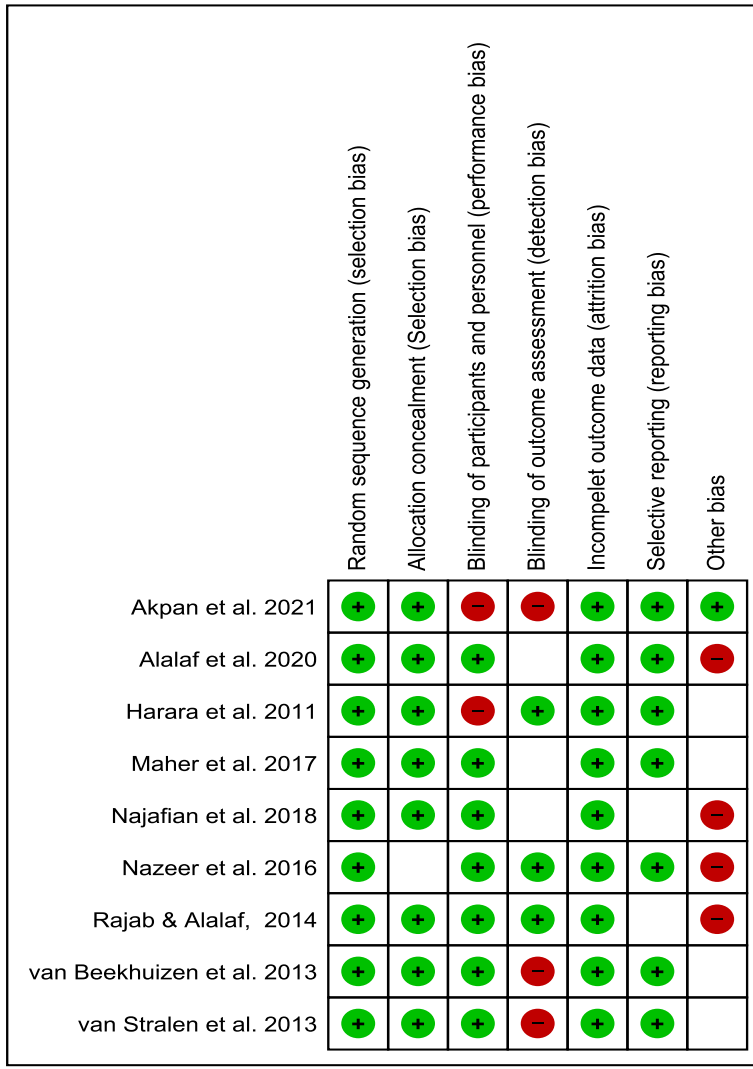

Figure (3): Bias risk summary.

4. Discussion

Most of the included studies in this review discussed intraumbilical vein injection of prostaglandin analogues for managing retained placenta. Six out of eight studies stated that prostaglandins, mainly misoprostol, were more effective than the comparator groups in decreasing blood loss [16, 17, 18] and requirement for manual placenta removal [16, 19]. Grillo-Ardila et al. also reported that by injecting prostaglandins intraumbilically, the necessity for physical placenta removal was reduced [27]. Another Cochrane systematic review [28] evaluated the use of

prostaglandins administered by any means other than intra-umbilical injection and found that their usage was associated with a lower incidence of severe postpartum hemorrhage, manual placenta removal, and blood transfusions. The explanation for the lack of statistical significance was that there wasn't enough power to verify the intervention's positive effects.

To treat retroplacental contractile disorders, uterotonics are injected through the umbilical vein, directly into the retroplacental myometrium [29, 30]. The use of umbilical vein injection of the saline solution alone or with oxytocin in contrast with expectant care, with another solution, or with another uterotonic drug for retained placentawas evaluated in a recent Cochrane study by Nardin et al. There were fifteen studies totaling 1,704 women with varying quality.

This review found that rectal administration of prostaglandin analogues (misoprostol) was effective in decreasing postpartum hemorrhage [22, 23, 24]. In a study on the drug absorption of misoprostol administered by different routes, Meckstroth et al. [31] discovered that the peak tone and peak uterine activity were lower after rectal administration, and the serum levels peaked earlier and decreased more abruptly. Thus, the rectal pharmacokinetics were preferred.

On the other hand, we found that sublingual [20, 21], oral [25], and vaginal administration of prostaglandin analogues were not effective in decreasing MRP or blood loss.

The safest and best care plan for retained placenta following vaginal birth need further randomized controlled studies. These will probably need to be big, multi-center studies with arms for both study drugs and placebo, based on the findings of this review. The most promising medications for further study, based on the facts at hand, are prostaglandin compounds, carbetocin, and intraumbilical injections of oxytocin.

5. Conclusion

In comparison with, oxytocin, oxytocin agonists, ergometrine, and placebo the use of prostaglandins through intraumbilical vein injection and rectally were superior and showed better results in managing retained placenta. To select which prostaglandin to use and at what dose for the medical management of retained placenta, more research is required.

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