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Maternal and neonatal complications of trial of labor after two cesarean sections (TOLAC-2) compared with repeat cesarean section (RCS-2): Systematic review and meta-analysis

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ABSTRACT

Title: Maternal and neonatal complications of the trial of labour after two caesarean sections (PPDC-2) versus repeat caesarean section (CR-2): Systematic review and meta-analysis.

Background: PPDC-2 is a behavior that is not accepted in all latitudes. Women who want natural childbirth do not receive the opportunity. The objective wasto conduct a systematic review and meta-analysis on the maternal and neonatal complications of PPDC-2 versus CR-2.

Methods: The eligibility criteria were: pregnant women of ≥22 weeks, two cesarean sections, cephalic presentation, no contraindications to natural delivery, no fetal malformations who undergo PPDC-2. We searched the libraries PubMed, Scopus, Embase and other websites of organisations linked to Obstetrics and Gynaecology. We assessed risk of bias using the Newcastle-Ottawa Scale. The Synthetic Method was used to summarize and present the results.

Results: The number of included articles that met the eligibility criteria was 10, with 3316 participants in the intervention group (PPDC-2) and 54054 in the control group (CR-2). The studies were cohort studies. The average success rate of PPDC-2 was 62.1%. There were no differences in maternal and neonatal complications in most publications. The rate of uterine rupture was very small.

Discussion: The information comes from good quality cohort studies (level of evidence 2b). PPDC-2 is a reasonable and relatively safe option, comparable to CR-2.

Others: It was financed with own resources, no protocol was carried out and it was not recorded on the basis of systematic reviews.

Keywords: *Vaginal delivery after two cesarean sections, maternal complications, neonatal complications.*

1. INTRODUCTION

Repeated caesarean sections are the main cause of the increase in the number of caesarean sections in the world. The repetition of cesarean sections caused a notable decrease in natural birth attempts after cesarean sections, mainly in low-income countries. Several reasons have been stated for the reduction in natural birth attempts: few health facilities and few obstetrician-gynecologists who provide vaginal delivery opportunities for patients with previous cesarean section, even if the previous cesarean section refuses to repeat the cesarean section.(1,2,3) (2,4,5) (1,2,5) (6)

Repeated cesarean sections are related to the fear of uterine rupture (UR), reported in the 70s and 80s in the United States of America (USA) and Europe, with medico-legal consequences; likewise, with medium and/or long-term complications, such

as the spectrum of placental accretism disorders, consequently hemorrhage before, during and after childbirth, a scenario that leads to maternal and neonatal morbidity and mortality, in addition to the surgical challenge of doctors specializing in gynecology and obstetrics.(1,7)(8) (1)(2,3,7)

The high rates of cesarean section on all continents, above 15%, a value recommended by the World Health Organization (WHO) and considered a turning point for the increase in maternal and neonatal morbidity and mortality, have placed the increased number of births per this way, in the worrying place, of Public Health problem. Combating the rapid increase in caesarean sections is one of the WHO's global goals. (9,10) (11,12,13)

Although there are encouraging results, published in the last two decades, of the Birth After Two C-sections Test (PPDC-2) and, in addition to the recommendation of the American College of Obstetricians and Gynecologists, issued in 2019, on the relevance and rationality of subjecting patients with two cesarean scars to a labor trial (2,14,15), medical specialists do not yet consider it safe and, Jamelle's phrase, "twice cesarean section, it is not always another cesarean section, but it is always a hospital birth" is not yet globalized. (16) (17)

Given this scenario, the question arises, are the maternal and neonatal complications of PPDC-2 comparable to those of repeated cesarean section? To answer the question, a systematic review of the literature and meta-analysis was carried out, with the aim of comparing maternal and neonatal complications of PPDC-2 and those derived from repeated cesarean section (CR-2).

2. METHODOLOGY

Women with a history of two cesarean sections with a low transverse segmental incision, gestational age greater than or equal to 22 weeks, cephalic presentation, no absolute contraindications to natural delivery, absence of fetal pathology before the onset of labor were included, and women with a history of two cesarean sections and unknown incision, history of non-obstetric uterine incision and fetus with uterine malformations were excluded.

La búsqueda se realizó en las bases de datos electrónicas: PubMed NIH MEDLINE (National Library of Medicine, desde 1980), Scopus Elsevier (desde 1980) y Embase Elsevier (desde 1980); además, se incluyó búsqueda en sitios web de organizaciones clave; Instituto Nacional for Clinical Excellence (NICE), Royal College of Obstetricians and Gynecologist (RCOG), American College of Obstetrician and Gynecologist (ACOG), Society of Obstetricians and Gynecologists of Canada (SOGC) y Revistas Médicas de Ginecología y Obstetricia (International Journal of Gynecology and Obstetrics, Obstetrics and Gynecology, American Journal of Obstetrics and Gynecology, American Journal of Perinatology, Journal of Obstetrics and Gynaecology Research, BJOG An International Journal of Obstetrics and Gynaecology, entre otras)

The terms included in the first search, carried out in the PubMed NIH MEDLINE electronic library, were the MeSH term(s): "vaginal birth after cesarean", where a large number of irrelevant articles were obtained (6486), Subsequently, a search was carried out in the same electronic library, using a combination of MeSH terms and other terms with the advanced search formula (((((complication, obstetric labor [MeSH Terms]) AND (trial of labor [MeSH Terms])) AND (cesarean section, repeat [MeSH Terms])) OR ("two cesareans"[Other Term])) OR ("two cesarean sections"[Other Term])) OR ("two previous cesarean sections"[Other Term]), where a large number of irrelevant articles were also obtained (142); however, 30 potentially relevant articles were chosen.

A third and fourth search was carried out in the Elsevier library, one in Scopus, using the following search formula ("complication"/exp OR complication) AND "trial of labor":ti.ab.kw AND "repeat cesarean section":ti.ab.kw OR "two cesareans":ti.ab.kw OR "two previous cesarean sections":ti.ab.kw ti.ab.kw and another in Embase, using the same search formula ("complication"/exp OR complication) AND "trial of labor": ti.ab.kw AND "repeat cesarean section":ti.ab.kw OR "two cesareans":ti.ab.kw OR "two cesarean sections":ti.ab.kw OR "two previous cesarean sections":ti.ab.kw, where 122 and 227 were obtained, most of them irrelevant, however, 33 and 15 relevant articles were chosen, respectively.

There were no language restrictions, but almost all articles were obtained in English. The search in electronic libraries and websites was complemented by the manual search of reference lists. Two relevant articles were obtained from the study references "Maternal and neonatal characteristics associated with clinical outcomes of TOLAC from 2012-20 in the USA: Evidence from a retrospective cohort study", no incluido en la revisión y meta-análisis, de los autores: Hanxu Shi, Siwen Li and collaborators, with doi: 10.1016/j.eclinm.2022.101681. eCollection 2022 Dec. In addition, a relevant article was obtained from the manual search in the Medical Journal "International Journal Gynecology and Obstetrics" with the phrase "vaginal birth after two cesarean sections". The The search was carried out until November 3, 2022, in the aforementioned databases.

The process of selecting studies and extracting data included five authors, who independently determined the relevance of the articles through titles, abstracts, methodology, and compliance with eligibility criteria. In addition, five review authors independently extracted data from each selected publication from the selected domains.

The assessment of risk of bias was carried out by five reviewers, who worked independently on each included study and used the Newcastle-Ottawa Scale. The articles were cohort design (nine retrospective and one prospective). There were no randomised clinical trials (RCTs) available on the subject. Case series, case publications, narrative reviews, duplicate articles, critical publications, and those that did not meet the eligibility criteria were excluded for the review. There was no language restriction.

We used the STROBE assessment tools to assess the publication quality of included studies (the study selection process and targeted search are shown in Figure 1). The details of each study are summarized in Table 1 (ten publications). To be included, all studies were judged to be of acceptable to good quality (level of evidence 2b), after risk of bias assessment and publication quality assessment.

The outcomes we looked for are primary maternal-neonatal outcomes and a secondary outcome mentioned below: successful PPDC-2, uterine rupture, hysterectomy, postpartum hemorrhage, Apgar score less than 7 at 5 minutes, and blood product transfusion; In addition, other primary outcomes such as surgical injury, febrile morbidity, maternal death, perinatal asphyxia, and neonatal death were searched but not considered in the analysis. We also looked for secondary outcomes such as: admission to maternal intensive care unit (ICU), neonatal ICU admission, prolonged hospital stay, but these were also not considered in the analysis.

For primary maternal and neonatal outcomes, the following definitions were used: Proof of delivery after two caesarean sections (PPDC-2) was defined as the consented intention of a patient who meets the eligibility criteria to opt for PPDC-2 and who achieves natural delivery without severe maternal and neonatal morbidity. Uterine rupture (UR) was defined as the solution of continuity of the three layers of the uterus (deciduous, muscle and serosa) in patients with two previous cesarean sections. Hysterectomy was defined as the removal of the uterine body or the uterus in its entirety after vaginal delivery or cesarean section in a patient with two previous cesarean sections. Postpartum haemorrhage (PPH) defined as blood loss of ≥500 mL independent of the birth route or ≥1000 mL during or after caesarean section in a woman with two previous caesarean sections. Blood product transfusion was defined as the administration of blood products to a patient undergoing PPDC-2 or CR-2. Apgar score of less than 7 at 5 minutes was defined as a score obtained after 5 minutes in the clinical evaluation of the newborn of a mother with two previous cesarean sections, regardless of the route of delivery.

To analyze the outcomes found and chosen, data were obtained directly from the ten included articles. Percentages were calculated according to the outcomes and the PPDC-2 success rate, RU rate, hysterectomy rate, PPH rate, blood product transfusion rate, and Apgar score rate less than 7 at 5 minutes were obtained. Outcomes were compared between the PPDC-2 and CR-2 cohorts and relative risk (RR) was calculated, statistical significance was analyzed by calculating a 95% confidence interval (CI) and an error of 5% was accepted. In addition, the calculation was performed with fixed or random effects, depending on the result of the heterogeneity test. The calculations and forest plots of each outcome (cohort of exposed versus cohort of unexposed) were performed with Review Manager 5.4.1 (RevMan 5.4.1) software for each outcome.

3. RESULTS

We identified ten articles in the different electronic medical libraries and websites for the final analysis. We reviewed 67 full-text articles and identified the ten articles from acceptable to good quality, which meet the eligibility criteria. The studies analyzed have a cohort design (nine retrospective and one prospective). There were no randomized clinical trials. Details of the studies included for review and meta-analysis are shown in Table 1. We excluded 51 studies due to the absence of keywords in the title or abstract and six articles were not retrieved in full text in the different citations or records. The process of selecting and identifying studies for review and meta-analysis is shown in Figure 1.

The studies that were used in data extraction and analysis included 3281 patients who attempted PPDC-2 and 54089 patients who chose CR-2. Data on the outcomes studied (PPDC-2 success rate, RU, hysterectomy, PPH, blood product transfusion, and Apgar score less than 7 at 5 minutes) were available in most articles, except for PPH which was not described in two studies, blood product transfusion which was not described in two studies, and neonatal outcome which was not available in two studies (Table 2.3 and 4).

Maternal and neonatal outcomes were assessed with vaginal delivery success rate, RU rate, hysterectomy rate, PPH rate, blood product transfusion rate, and Apgar score rate less than 7 at 5 minutes. Other morbidities or outcomes such as prolonged hospital stay, surgical injuries, admission to the maternal intensive care unit (NICU), admission to the neonatal intensive care unit (NICU) were variably classified and very diverse for the combined analysis.

Percentages were calculated based on data from studies that reported the outcomes analysed. Table 1 shows the details of the included studies. Table 2 shows the maternal and neonatal complications of PPDC-2, Table 3 shows the maternal and neonatal complications of CR-2, and Table 4 shows the comparison of maternal and neonatal complications of PPDC-2 versus CR-2.

Figure 1. Review and Meta-analysis: Maternal and neonatal complications of PPDC-2 versus CR-2.

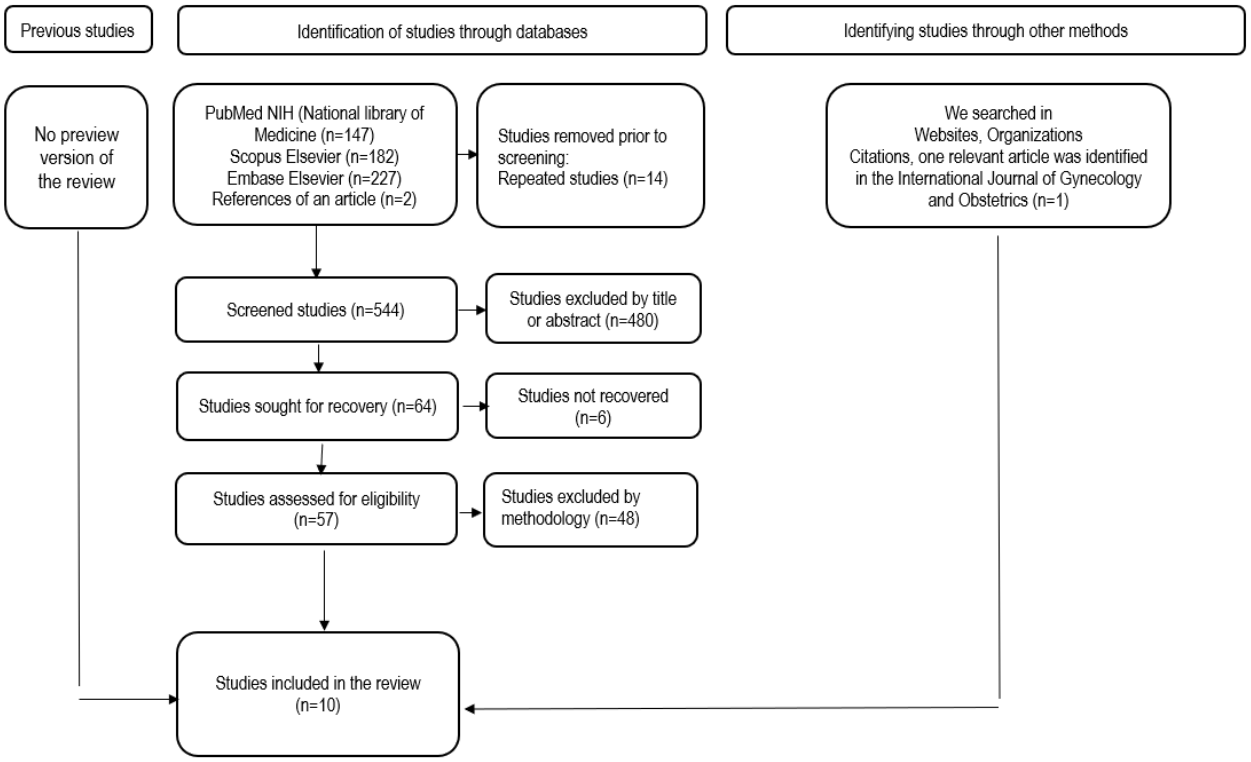

Figure 1. Review and Meta-analysis: Maternal and neonatal complications of PPDC-2 versus CR-2.

Table 1. Details of studies included for the Review and Meta-analysis: Maternal and neonatal complications of PPDC-2 versus RCS-2.

Baseline Study	Study population	Methodology	Success rate	Maternal complications	Neonatal complications
Suspenders (France), 2001	180 patients with two previous non-vertical scars, single fetus in cephalic, with an estimated weight of less than 4000 g, normal pelvic dimensions, of which 94 patients accepted proof of labor and 86 patients with the same characteristics decided to repeat the cesarean section.	Retrospective cohort design, 6 years, from 1990 to 1995.	65.6% of patients with two previous cesarean scars had a successful vaginal delivery.	There were no uterine ruptures or maternal deaths (0/94) in the exposed cohort (PPDC-2) or (0/86) in the non-exposed cohort (CR-2). One case (1/94) of hysterectomy in the PPDC-2 cohort versus no cases (0/86) in the CR-2 cohort. Two cases (2/94) of postpartum hemorrhage in the PPDC-2 cohort versus no cases (0/86) in the CR-2 cohort. In two cases (2/94), blood products were transfused in the PPDC-2 cohort compared to no cases (0/86) in the CR-2 cohort. There were no significant differences in the maternal outcomes of the exposed group	There were no cases (0/94) of infants with an Apgar score of less than 7 at 5 minutes in the exposed cohort (PPDC-2) or (0/86) in the non-exposed cohort (CR-2). No neonatal deaths in both cohorts.

				compared to those of the non-exposed group.	
De Leo (Italy), 2020	114 patients with a history of two cesarean sections, with a single fetus, absence of morphological abnormalities and contraindications to vaginal delivery, of which 46 patients attempted labor testing and 68 patients with the same characteristics chose to repeat cesarean section.	Retrospective Cohort Design, 9 years, from 2011 to 2019.	76.1% of patients with two previous cesarean sections had a successful vaginal delivery.	There was one case (1/46) of uterine rupture in the PPDC-2 cohort versus no cases (0/68) in the CR-2 cohort. There were no cases of hysterectomy, postpartum hemorrhage, or blood product transfusion in both cohorts. There were no significant differences in the maternal outcomes of the exposed group compared to those of the non-exposed group.	There was one case (1/46) of Apgar score less than 7 at 5 minutes in the PPDC-2 cohort versus no cases (0/68) in the CR-2 cohort. No neonatal deaths in both cohorts
Dombrowski (EUA), 2020	42771 patients with two previous cesarean sections, single fetus, absence of congenital anomalies, no contraindications for vaginal delivery, of which 1228 women attempted vaginal delivery and 41543 women decided to repeat cesarean section.	Retrospective Cohort Design, 3 years, 2010 to 2012.	39.4% of patients with two previous cesarean sections had a successful vaginal delivery.	There was one case (1/1228) of uterine rupture in the PPDC-2 cohort versus no cases (0/41543) in the CR-2 cohort. One case (1/1228) of hysterectomy in the PPDC-2 cohort versus no cases (0/41543) in the CR-2 cohort. There were no cases of postpartum hemorrhage in both cohorts. 1006 cases of postpartum hemorrhage (1006/1228) in the PPDC-2 cohort versus 33830 cases (33830/41543) in the CR-2 cohort. There were no significant differences in the maternal outcomes of the exposed group compared to those of the non-exposed group.	There was one case (1/1228) of Apgar score less than 7 at 5 minutes in the PPDC-2 cohort versus no case (0/41543) in the CR-2 cohort. No neonatal deaths in both cohorts.
Garg, 2004	205 patients with two previous cesarean sections, singleton fetus, placenta previa, absence of vertical cesarean section scars or non-obstetric uterine scars, of which 101 women attempted vaginal delivery and 104 women decided to repeat cesarean section.	Retrospective Cohort Design, 6 years, 1997 to 2002	Vaginal delivery success rate was 65.3%.	There were no cases (0/101) of uterine rupture in the PPDC-2 cohort versus one case (1/105) in the CR-2 cohort. There were no cases of hysterectomy in both cohorts. There were three cases (3/101) in the PPDC-2 cohort versus eight cases (8/104) in the CR-2 cohort. There were no cases (0/101) of blood product transfusion in the	There was one case (1/101) Apgar score less than 7 at 5 minutes in the PPDC-2 cohort versus no case (0/104) in the CR-2 cohort. No neonatal deaths in both cohorts.

				PPDC-2 cohort versus eight cases (8/104) in the CR-2 cohort. There were no significant differences in the maternal outcomes of the exposed group compared to those of the non-exposed group.	
Horgan (EUA), 2022	793 patients with no history of uterine rupture, with two previous cesarean sections, without successful vaginal delivery after the two cesarean sections, single fetus without abnormalities, cephalic presentation, absence of classic scar or myomectomy scar, absence of placenta previa or suspicion of accretism, of which 82 women accepted the vaginal delivery modality and 711 women decided to repeat the cesarean section.	Retrospective Cohort Design, 11 years, 2008 to 2018.	69.5% of patients with two previous cesarean sections had a successful vaginal delivery.	There was one case (1/82) of uterine rupture in the PPDC-2 cohort versus no cases (0/711) in the CR-2 cohort. There were no cases (0/82) of hysterectomy in the PPDC-2 cohort versus one case (1/711) in the CR-2 cohort. There were three cases (3/82) of postpartum hemorrhage in the PPDC-2 cohort versus 52 cases (52/711) in the CR-2 cohort. There were two cases (2/82) in the PPDC-2 cohort versus 15 cases (15/711) in the CR-2 cohort. There were no significant differences in the maternal outcomes of the exposed group compared to those of the non-exposed group.	There were no cases (0/82) of Apgar score less than 7 at 5 minutes in the PPDC-2 cohort versus one case (1/711) in the CR-2 cohort. No neonatal deaths in both cohorts.
Macones (USA), 2005	3970 patients with two previous cesarean sections, of which 1082 women accepted the vaginal delivery modality and 2888 women decided to repeat the cesarean section.	Retrospective, multicenter, record-based Cohort Design, 5 years, 1996 to 2000	74.6% of patients who underwent labor ended in successful vaginal delivery.	There were 19 cases (19/1082) of uterine rupture in the PPDC-2 cohort versus one case (1/2888) in the CR-2 cohort. There were no cases of hysterectomy in both cohorts. Ten cases (10/1082) of postpartum hemorrhage in the PPDC-2 cohort versus no cases (0/2888) in the CR-2 cohort. Ten cases (10/1082) of blood product transfusion in the PPDC-2 cohort versus 34 cases (34/2888) in the CR-2 cohort. There were no significant differences in the maternal outcomes of the exposed group compared to those of the non-exposed group.	There is no data on Apgar scores.
Miller (EUA), 2015	6162 patients, with two previous low	Prospective Cohort Design.	65% of patients who	There was one case (1/152) of uterine	There were no cases (0/82) of

	transverse segmental cesarean sections, with a history of successful vaginal delivery, single fetus in cephalic without abnormalities and weight less than 4000g, of which 152 women accepted the vaginal delivery modality, of spontaneous onset and normal progression and 6010 women decided to repeat the cesarean section.		attempted vaginal delivery had a successful vaginal delivery.	rupture in the PPDC-2 cohort versus seven cases (7/6010) in the CR-2 cohort. There were no cases (0/152) of hysterectomy in the PPDC-2 cohort versus 22 cases (22/6010) in the CR-2 cohort. There were three cases (3/152) of postpartum hemorrhage in the PPDC-2 cohort versus no cases (0/6010) in the CR-2 cohort. There were three cases (3/152) of blood product transfusion in the PPDC-2 cohort versus 105 cases (105/6010) in the CR-2 cohort. There were no significant differences in the maternal outcomes of the exposed group compared to those of the non-exposed group.	Apgar score less than 7 at 5 minutes in the PPDC-2 cohort versus one case (1/711) in the CR-2 cohort. There was one neonatal death in the PPDC-2 cohort versus 13 in the CR-2 cohort.
Modzelewski (Poland), 2019	406 patients with two previous cesarean sections, a single fetus without abnormalities in cephalic presentation, absence of placenta previa, of which 35 women accepted the vaginal delivery modality and 371 women decided to repeat the cesarean section.	Retrospective Cohort Design, 8 years, from 2010 to 2017.	62.85% of patients who opted for labor trial had a successful vaginal delivery.	There were no cases (0/35) of uterine rupture in the PPDC-2 cohort versus 11 cases (11/371) in the CR-2 cohort. There were no cases of hysterectomy in both cohorts. There were four cases (4/35) of postpartum hemorrhage in the PPDC-2 cohort versus five cases (5/371) in the CR-2 cohort. One case (1/35) of blood product transfusion in the PPDC-2 cohort versus three cases (3/371) in the CR-2 cohort. There were no significant differences in the maternal outcomes of the exposed group compared to those of the non-exposed group.	No data on Apgar score
Poloni, 2012	50 patients with a history of two caesarean sections, of which 11 patients requested proof of labour and 39 chose to repeat caesarean section.	Retrospective Cohort Design, 5 years, from 2008 to 2012.	The success rate of vaginal delivery was 72.7% (9).	There were no cases of uterine rupture, hysterectomy, postpartum hemorrhage, or blood product transfusion in both cohorts. There were no significant differences in the maternal outcomes of	There were no cases of neonates with an Apgar score of less than 7 at 5 minutes in the exposed cohort (PPDC-2) or in the non-exposed cohort (CR-2). No neonatal deaths in both cohorts. There

				the exposed group compared to those of the non-exposed group.	were no fetal or neonatal deaths.
Rotem (Israel), 2020	2719 patients with two previous low transverse segmental cesarean sections, single fetus in cephalic, non-macrosomic, low transverse, absence of placenta previa or accretism, of which 485 women requested proof of labor and 2234 women decided to repeat the cesarean section.	Retrospective Cohort Design, 15 years, from 2005 to 2019.	86.2% of patients who opted for labor trial had a successful vaginal delivery.	There were three cases (3/485) of uterine rupture in the PPDC-2 cohort versus three cases (3/2234) in the CR-2 cohort. There was one case of hysterectomy (1/485) in the PPDC-2 cohort versus two cases (2/2234) in the CR-2 cohort. There were 35 cases (35/485) of postpartum hemorrhage in the PPDC-2 cohort versus 167 cases (167/2234) in the CR-2 cohort. There were eight cases (8/485) of blood product transfusion in the PPDC-2 cohort versus 58 cases (58/2234) in the CR-2 cohort. There were no significant differences in the maternal outcomes of the exposed group compared to those of the non-exposed group (CR-2).	There were nine cases (9/485) of Apgar score less than 7 at 5 minutes in the PPDC-2 cohort versus 45 cases (45/2234) in the CR-2 cohort.

Table 2. Maternal and neonatal complications of PPDC-2 in the studies included for the Review and Meta-analysis.

Baseline Study	Cohort	Number	Success rate	Rotura is Uterina	Hysterectomy	Hemorrhage posparto	Transfusion of blood products	Apgar score < 7 at 5 minutes
Bretelle, 2001	PPDC-2	94	63 (67%)	0 (0.0%)	1 (1.1%)	2 (2.1%)	1 (1.1%)	0 (0.0%)
De Leo, 2020	PPDC-2	46	35 (76.1%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	-	1 (2.2%)
Dombrowski, 2020	PPDC-2	1228	484 (39.4%)	1 (0.08%)	1 (0.08%)	0 (0.0%)	-	1 (0.08%)
Garg, 2004	PPDC-2	101	66 (65.3%)	0 (0.0%)	0 (0.0%)	3 (3.0%)	0 (0.0%)	9 (8.9%)
Horgan, 2022	PPDC-2	82	57 (69.5%)	1 (1.2%)	0 (0.0%)	3 (3.7%)	2 (2.4%)	0 (0.0%)
Macones, 2005	PPDC-2	1082	807 (74.6%)	19 (1.76%)	0 (0.0%)	.	10 (0.9%)	-
Miller, 2015	PPDC-2	152	99 (65.1%)	1 (0.7%)	0 (0.0%)	.	3 (2.0%)	3 (2.0%)
Modzelewski, 2019	PPDC-2	35	22 (62.9%)	0 (0.0%)	0 (0.0%)	4 (11.4%)	1 (2.9 %)	0 (0.0%)
Poland, 2012	PPDC-2	11	09 (81.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Rotem, 2020	PPDC-2	485	418 (86.2%)	3 (0.6%)	1 (0.2%)	35 (7.2%)	8 (1.6%)	9 (1.9%)
All studies	PPDC-2 Total	3316	2060 (62.1%)	26 (0.8%)	03 (0.09%)	47/2082 (2.3%)	25/2042 (1.2%)	23/2223 (1.0%)

Table 3. Maternal and neonatal complications of CR-2 in the studies included for the Review and Meta-analysis.

Baseline Study	Cohort	Number	Rotura is Uterina	Hysterectomy	Hemorrhage posparto	Transfusion of blood products	Apgar score < 7 at 5 minutes
Bretelle, 2001	CR-2	86	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
De Leo, 2020	CR-2	68	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)
Dombrowski, 2020	CR-2	41543	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)
Garg, 2004	CR-2	104	1 (1.0%)	0 (0.0%)	8 (7.7%)	8 (7.7%)	9 (8.7%)
Horgan, 2022	CR-2	711	0 (0.0%)	1 (0.1%)	52 (7.3%)	15 (2.1%)	1 (0.1%)
Macones, 2005	CR-2	2888	1 (0.03%)	0 (0.0%)	.	34 (1.2%)	-
Miller, 2015	CR-2	6010	7 (0.1%)	22 (0.4%)	.	105 (1.7%)	51 (0.8%)
Modzelewski, 2019	CR-2	371	11 (3%)	0 (0.0%)	5 (1.3%)	3 (0.8%)	0 (0.0%)
Poland, 2012	CR-2	39	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Rotem, 2020	CR-2	2234	3 (0.1%)	2 (0.1%)	167 (7.5%)	58 (2.6%)	45 (2.0%)
Baseline studies	Cohorte total CR-2	54054	23 (0.04%)	25 (0.05%)	232/45191 (0.5%)	223/12478 (1.8%)	106//51127 (0.2%)

Table 4. Maternal and neonatal complications of PPDC-2 versus CR-2 in the studies included for the Review and Meta-analysis.

Baseline Study	Cohorts	Number	Rotura is Uterina	Hysterectomy	Hemorrhage posparto	Transfusion of blood products	Apgar score < 7 at 5 minutes
Bretelle, 2001	PPDC-2	94	0 (0.0%)	1 (1.1%)	2 (2.13%)	1 (1.1%)	0 (0.0%)
	CR-2	86	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
De Leo, 2020	PPDC-2	46	1 (2.2%)	0 (0.0%)	0 (0.0%)	-	1 (2.2%)
	CR-2	68	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Dombrowski, 2020	PPDC-2	1228	1 (0.08%)	1 (0.08%)	0 (0.0%)	-	1 (0.08%)
	CR-2	41543	0 (0.0%)	0 (0.0()	0 (0.0%)		0 (0.0%)
Garg, 2004	PPDC-2	101	0 (0.0%)	0 (0.0%)	3 (3.0%)	0 (0.0%)	9 (8.9%)
	CR-2	104	1 (1.0%)	0 (0.0%)	8 (7.7%)	8 (7.7%)	9 (8.7%)
Horgan, 2022	PPDC-2	82	1 (1.2%)	0 (0.0%)	3 (3.7%)	2 (2.4%)	0 (0.0%)
	CR-2	711	0 (0.0%)	1 (0.1%)	52 (7.3%)	15 (2.1%)	1 (0.1%)
Macones, 2005	PPDC-2	1082	19 (1.8%)	0 (0.0%)	.	10 (0.9%)	-
	CR-2	2888	1 (0.03%)	0 (0.0%)		34 (1.2%)	
Miller, 2015	PPDC-2	152	1 (0.7%)	0 (0.0%)	.	3 (2.0%)	3 (2.0%)
	CR-2	6010	7 (0.12)	22 (0.4%)		105 (1.7%)	51 (0.8%)
Modzelewski, 2019	PPDC-2	35	0 (0.0%)	0 (0.0%)	4 (11.4%)	1 (2.9%)	0 (0.0%)
	CR-2	371	11 (3.0%)	0 (0.0%)	5 (1.3%)	3 (0.8%)	0 (0.0%)
Poland, 2012	PPDC-2	11	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
	CR-2	39	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Rotem, 2020	PPDC-2	485	3 (0.6%)	1 (0.2%)	35 (7.2%)	8 (1.6%)	9 (1.9%)
	CR-2	2234	3 (0.1%)	2 (0.1%)	167 (7.5%)	58 (2.6%)	45 (2.0%)

Successful vaginal delivery was achieved in 2060 patients out of 3316 (62.1%) women with a history of two cesarean sections who opted for the natural delivery test, corresponding to the 10 studies included in the review and meta-analysis, as shown in tables 1 and 2, with a variation in the rate between the studies reporting from 39.4 to 86%. The analysis of this outcome is not comparable with the RCS-2 group, for obvious reasons.

The rate of UR in women with PPDC-2 was reported in all included studies. Comparative analysis between the PPDC-2 and CR-2 groups in all included studies revealed RU rates of 0.8% (26/3316) in PPDC-2 versus 0.04% (23/54054) in RCS-2, with a variation between studies of 0 to 2.2% for PPDC-2 and 0 to 3.0% for CR-2. The meta-analysis showed a combined RR = 6.55 of RU in the PPDC-2 group versus CR-2, CI: 1.81-23.70 (Figure 2, p = 0.004, Z = 2.87).

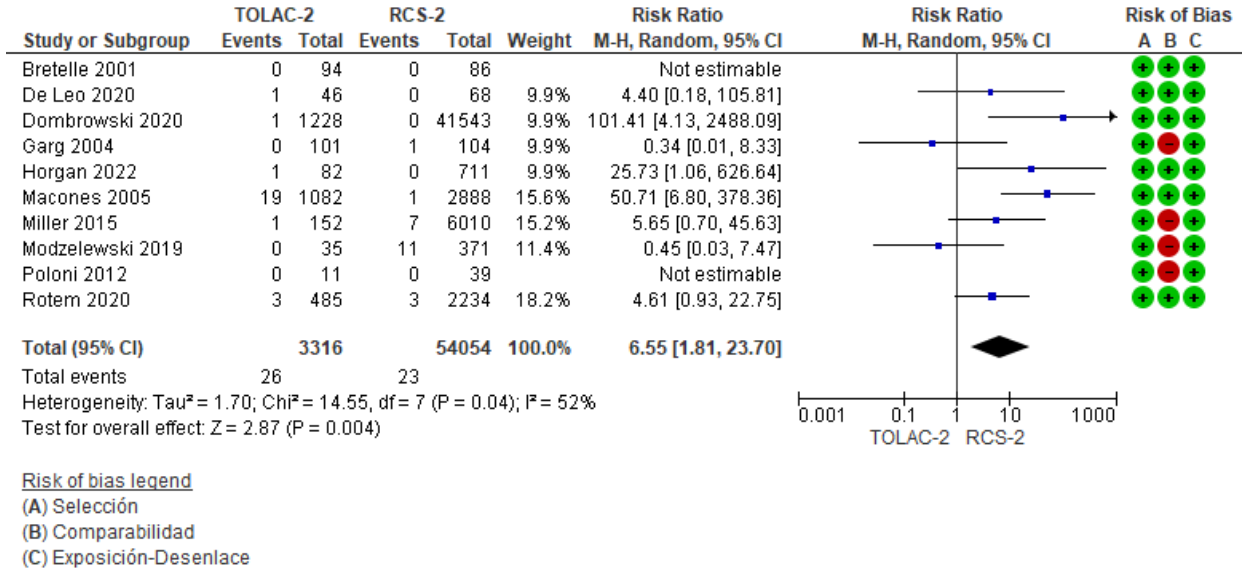

Figure 2. Uterine rupture of PPDC-2 versus CR-2.

There was a higher rate of RU in the PPDC-2 cohort; CR-2 did not seem to protect against the occurrence of UR, the cases described in the studies correspond to asymptomatic and symptomatic uterine ruptures, because in some cases no discomfort is described and in others symptoms are described for suspicion before planned or scheduled surgery and, although possible, it was a finding during the surgical procedure that was not expected.

The rate of hysterectomy was reported in all included studies. The comparison figures between the PPDC-2 and CR-2 groups were 0.09% (3/3316) and 0.05% (25/54054) respectively. The meta-analysis showed a combined RR = 3.88 of hysterectomy in the PPDC-2 versus CR-2 group, CI: 0.84-17.90 (Figure 3, p = 0.08, Z = 1.74).

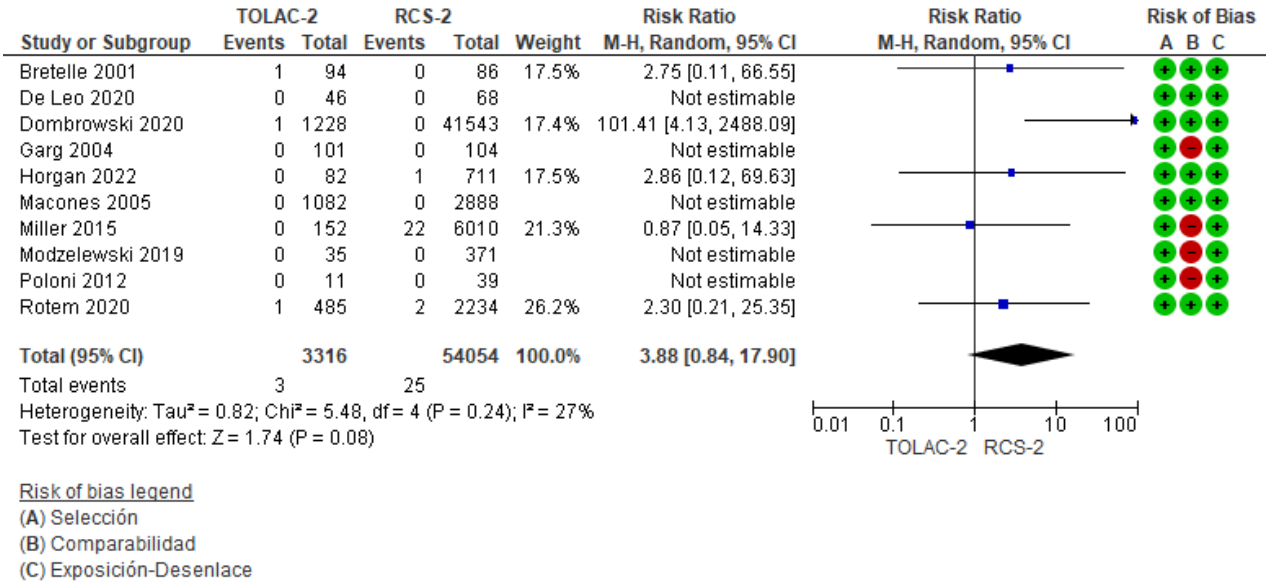

Figure 3. PPDC-2 versus CR-2 hysterectomy.

The rate of PPH was reported in all included studies. The comparison figures between the PPDC-2 and CR-2 groups were 2.3% (47/2082) and 0.5% (232/45191) respectively. The meta-analysis showed a pooled RR=1.23 of postpartum hemorrhage in the PPDC-2 versus CR-2 group, CI: 0.46-3.30 (Figure 4, p=0.68, Z=0.41).

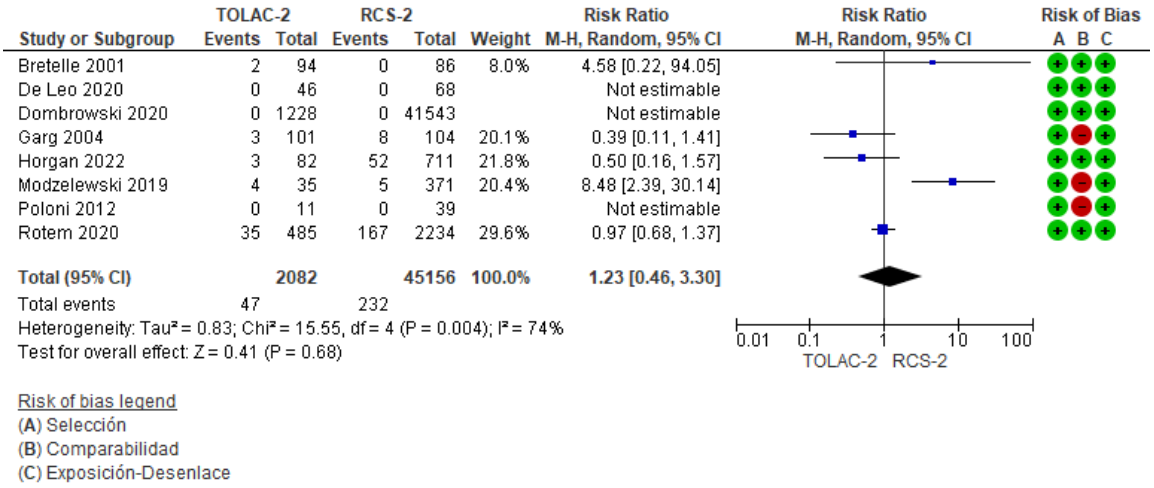

Figure 4. Postpartum hemorrhage of PPDC-2 versus CR-2.

The rate of blood product transfusion was reported in all but one of the included studies. The comparison figures between the PPDC-2 and CR-2 groups were 1.2% (25/2042) and 1.8% (223/12478) respectively. The meta-analysis showed a combined RR = 0.72 of blood product transfusion in the PPDC-2 versus CR-2 group, CI: 0.48-1.08 (Figure 5, p = 0.11, Z = 1.59).

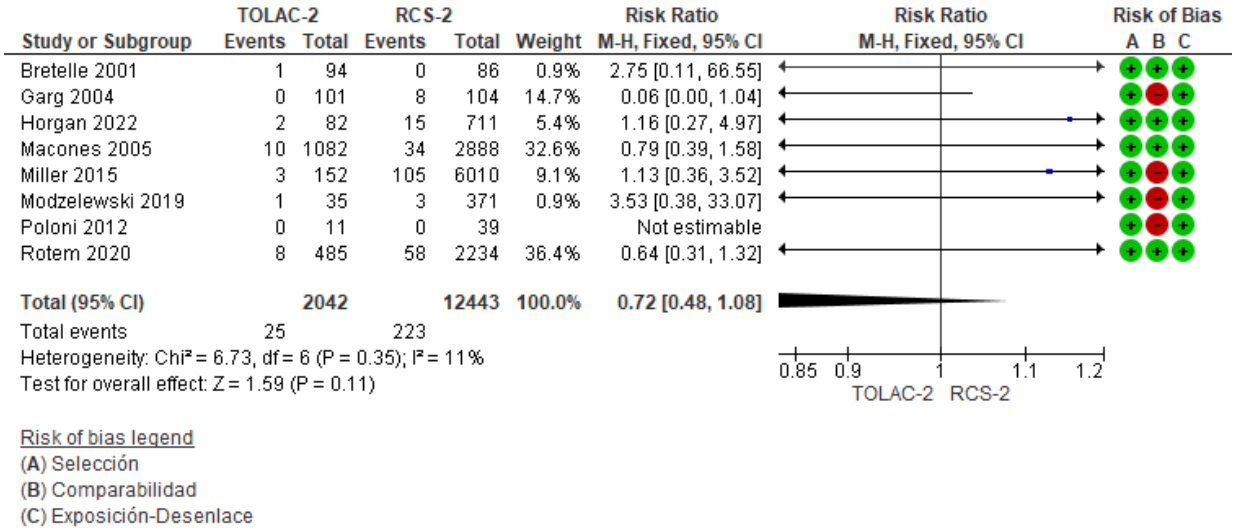

Figure 5. Transfusion of PPDC-2 versus CR-2 blood products.

Neonatal outcome of an Apgar score of less than 7 at 5 minutes was reported in 8 included studies. The comparison figures between the PPDC-2 and CR-2 groups were 1.0% (23/2223) and 2.0% (106/51127) respectively. The meta-analysis showed a pooled RR = 1.82 Apgar score less than 7 at 5 minutes in the PPDC-2 versus CR-2 group, CI: 0.78-4.24 (Figure 6, p = 0.16, Z = 1.40).

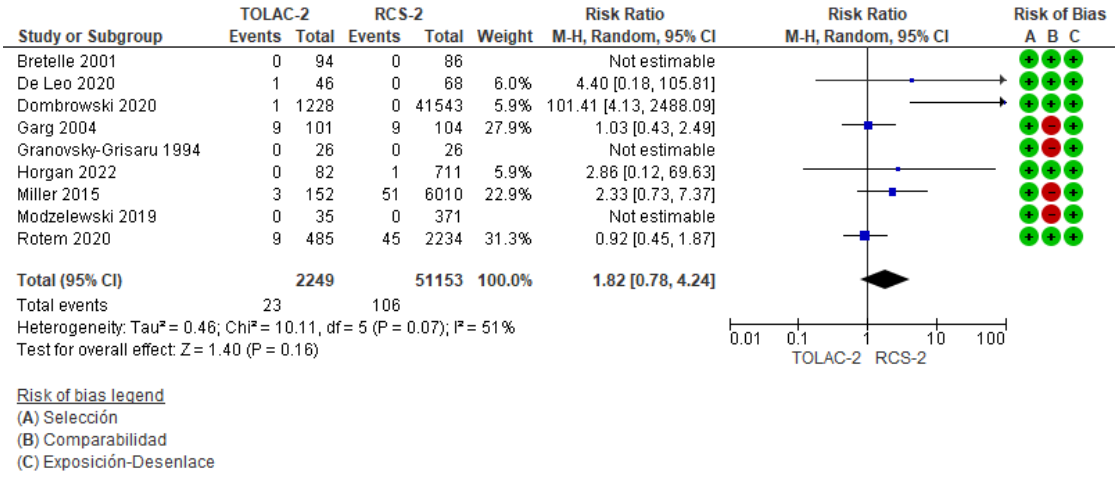

Figure 5. Apgar score less than 7 at 5 minutes for PPDC-2 versus CR-2.

4. DISCUSSION

The intent of PPDC-2 varies among the studies included in the review, from 2.9% for Dombrowski to 52.2% for Bretelle. The variation is likely due to the difference in intent to offer PPDC-2, the willingness of physicians at health facilities to provide guidance and information about the risks and benefits of PPDC-2, or the facility's policy. (18) (2) (1)

The review shows that PPDC-2 is associated with a reasonable success rate (62.1%). The maternal complications analyzed (hysterectomy, PPH and blood product transfusion) of PPDC-2 are comparable with the CR-2 group, with similar rates of hysterectomy (p=0.08), (PPH) (p=0.48) and transfusion of blood products (p=0.2) and different rates of RU (p=0.002).

The neonatal complications analysed in the included studies are heterogeneous with respect to outcomes. The neonatal outcome that matched in seven studies included in the review was an Apgar score of less than 7 at 5 minutes. For this reason, the analysis was limited to this outcome. There was no significant difference between the PPDC-2 and CR-2 groups. (p=0.06).

The medical professional's unwillingness to offer a PPDC-2 is likely due to concerns about the risk of RU due to scarring. UR is a rare complication and study publications show limitations, mainly due to sample size, which makes it difficult to assess it as an adverse outcome in patients with this condition. (1,2,19) (1,19)

Pooled data analysis provides more reliable figures. The rate of UR in the pooled analysis was 0.8% for PPDC-2 (Table 2), values similar to those reported by leading institutions such as the American College of Obstetricians and Gynecologists (ACOG) and the French College of Obstetricians and Gynecologists (CNGOF). All studies included in the review provided figures for the UK. . (1,19)(7,19)

The studies that contributed with the greatest weight in the meta-analysis provide different rates (1.8%, 0.7% and 0.0%), the highest corresponded to a large number of participants (1082), a figure that is above the average for this analysis and for the reports of world institutions; however, the other studies of similar weight present figures within reported ranges, with fewer participants.(20,21,22) (20) (19,1)(1,19)

In four studies, the management of PPDC-2 was superficially described. The use of oxytocin alone, oxytocin with epidural analgesia or with the use of an intracervical Foley tube are common practice in these studies, following the recommendations of the ACOG. The association between the management of PPDC-2 and the UK was not analyzed in the included studies because of the diversity in it. (2,20,21,22) (20,21)(2) (22) (1)(2,20,21,22)

The UR in CR-2 resulted in 0.04%, despite the fact that it was expected that opting for CR-2 would not occur this event. The relative risk (RR) of RU was 6.55, CI:1.85-23.70, (p=0.004) of PPDC-2 versus CR-2; although there is statistical significance, they are very small numbers and maternal morbidity is not significant, as mentioned by Caughey and the authors of the included studies. (3) (2,16,20,21,22,18,23,24,25)

The overall hysterectomy rate was 0.09%. The hysterectomy rates of PPDC-2 and CR-2 are comparable (0.09% and 0.05%, respectively) and are similar, with no statistically significant difference (p=0.08), as shown in all studies included in the meta-analysis, except one, in which a higher risk is reported for the PPDC-2 group. The relative risk (RR) of hysterectomy was 3.88, CI:0.84-1790, (p=0.008) of PPDC-2 versus CR-2. The result coincides with the reports of the ACOG and the CNGOF. (2,20,21,22,26,16,24,25) (18) (1,19)

The PPH rate was 2.3% and 0.5% in PPDC-2 and CR-2, respectively, resulting in similar results to the meta-analysis (p=0.48), with an RR=1.23, CI:0.46-3.30; however, when breaking down the rate of postpartum hemorrhage in the included studies, we can show that of the four articles with the greatest weight in the meta-analysis, only one reports statistical significance in favor of CR-2. (22,26,25,23)(22)

It should be noted that Modzelewski's results show a lower bleeding rate in patients with successful PPDC-2, compared to CR-2; however, when the subgroups (successful PPDC-2, failed PPDC-2, scheduled CR-2, and unscheduled CR-2) are compared, the highest rate of PPH corresponds to failed PPDC-2. In addition, there was an increased need for hemostatic procedures not described in unscheduled CR-2. (22)

Horgan reports different results from Modzelewski, when comparing PPDC-2 versus programmed CR-2, with PPDC-2 being the group with the lowest rate of PPH (including failed PPDC-2); however, when the subgroups (successful PPDC-2 and failed PPDC-2) of PPDC-2 are compared, the results show significant differences between both groups in favor of successful PPDC-2. It did not present data on patients undergoing unscheduled CR-2. (23) (22)

It is important to mention that postpartum hemorrhage is defined as the blood loss of 500 ml after delivery, regardless of the route; but there are other definitions for HPP via cesarean section. The Australian College of Obstetricians defines it as blood loss greater than 750 ml in caesarean section; Likewise, the most common definition is blood loss equal to or greater than 1000 ml during cesarean section (27) (27,28).

Most of the articles included do not describe the definitions of HPP used to consider it as such. The use of a different definition of PPH depending on the route may explain the different rates when comparing both groups (2.3% vs. 0.5%, p=0.48), as they present a higher probability of obtaining a case, with a lower volume of blood loss in the intervention group.

The PPH results of our meta-analysis differ very significantly from the studies of Magann and Naef, who report higher rates after cesarean section (0.5% vs. 5.8 and 7.9%, respectively), with different quantification and different amounts. Magann, estimates it above 1000ml and Naef estimates it above 1500 ml.(29) (30) (29)(30)

Pont reports significantly higher rates of PPH in patients who opt for trial of labor after cesarean section (PPDC) and in patients with elective repeat cesarean section (RC) compared to our results (9.3% and 5.4% vs. 2.3% and 0.5%). It should be noted that it does not mention the number of cesarean sections, but these are data to consider due to the difference in the figures.(31)

The transfusion rate of blood products was 1.2% and 1.8% in PPDC-2 and CR-2, respectively, with similar and comparable results (p=0.2). In all studies included in the analysis, there was no significant difference. The need for transfusion is an indirect measure of blood loss and, in our meta-analysis, corresponds to the outcome of the PPH outcome. (28)

It should be noted that the transfusion of blood products was not detailed in any of the studies included in the review and meta-analysis. The type of blood products, the number of blood products used, and the severity of PPH to cover the need for transfusion are not reported. Disaggregating the information would help us to classify maternal morbidity and obtain the necessary means for the management of PPH.

The Apgar score rate of less than 7 at 5 minutes was 1.1% and 0.2%, respectively, with similar results (p=0.06). In three included studies, the heaviest ones, they show similar results in both groups. Other complications such as neonatal asphyxia or transient tachypnea of the newborn were not analyzed; however, Thaseen reports similarity of results between the groups. (21,26,25) (32)

It should be noted that reliability depends on factors, such as the accuracy of the estimation and the suitability of the research design. The information comes from moderate- to good-quality cohort studies, which provide our evidence (level of evidence 2b); however, we had limitations in the review process and evidence of the review, which we will mention below.

The publications considered for the review and meta-analysis belong to broad periods of time, where the behavior may vary due to temporality (2001 to 2022). Currently, the rate of cesarean sections is high, consequently, the participants of the recently published studies could represent biased populations, where only selected patients or patients who decide and request a PPDC-2 are chosen.

The studies included in the review and meta-analysis, although it is true, mention accentuation as a common practice, do not detail the management of labor, which could lead us to think of a different management of labor (use of oxytocin without analgesia, use of oxytocin with analgesia, use of Foley tube or use of prostaglandins) that do not allow associating the management of labor with complications.

The proportion of participants who meet the eligibility criteria for each study are selected by the research team or voluntarily request, self-motivated, the PPDC-2, varies from 2.9% to 52.2% among the studies, which could be an indication of heterogeneous selection; likewise, some articles included women with more than two cesarean sections, although for the purposes of this study, only the analyzed comparison was used.

The control group chosen in the included studies was made up of women who decided to repeat cesarean section, regardless of their favorable characteristics for PPDC-2 (previous vaginal delivery, vaginal delivery between cesarean sections, vaginal delivery after two cesarean sections, advanced vaginal labor, among others), were also variable, where the common point was rejection of PPDC-2 and more precise results could not be obtained.

Excessive conceptualization of positive results of PPDC-2 in the existing literature is possible, an inherent limitation of meta-analyses of observational studies; however, in the absence of randomised trials (RCTs) on the subject, prospective or retrospective cohorts are reasonable available evidence of success rate and risks.

The answer to the question: Are the maternal and neonatal complications of PPDC-2 comparable to those of CR-2? It has implications in classic obstetric practice, in future research and in health policies. This review and meta-analysis shows the evidence on the success rate and risk of maternal and neonatal complications of PPDC-2 versus CR-2.

The classic obstetric practice of repeating a cesarean section due to the history of two cesarean sections, without considering clinical factors, is a behavior still rooted, mainly in medical professionals in Latin America and the Caribbean, which could change course with the results of this meta-analysis, if it is considered that, on average, 6 out of 9 patients with PPDC-2 achieve a successful PPDC-2. among other results comparable to CR-2. (1)

The results of this meta-analysis have implications for the informed decision of women and their families, together with physicians, since they represent reliable data on the risks and benefits attributable to each route of delivery; although there is no direct evidence on them in the PPDC-2, it is the product of the sum of publications with cohort design that provide evidence comparable to those from the CR-2.

There is comparable evidence, according to the results of this meta-analysis, for PPDC-2 and CR-2; however, we need high-quality research with a selective approach, in order to obtain greater success and/or fewer complications; likewise, to obtain detailed information on the process and more precise conclusions, which help us to propose preventive measures and policies to improve maternal-perinatal health. (2)

5. CONCLUSIONS

Vaginal delivery after two cesarean sections is a reasonable and relatively safe option, comparable to repeated cesarean section, in certain conditions such as: low segmental previous incisions, the patient's will, the predisposition of health professionals, among the most prominent.

OTHER INFORMATION

The review is not recorded in a review database. No protocol for the review was drafted.

It was financed with its own resources. There is no conflict of interest.

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