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Original Research Article

Effectiveness, safety, and acceptability of postplacental insertion of GyneFix postpartum intrauterine device among women undergoing cesarean section: A multicenter prospective cohort study in China☆,☆☆

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ABSTRACT

Objectives: To assess the effectiveness, safety, and acceptability of postplacental insertion of GyneFix postpartum intrauterine device (PPIUD) in women undergoing cesarean section (C-section).

Study design: We conducted a prospective cohort study at 14 hospitals in four eastern coastal provinces of China between September 2017 and November 2020. A total of 470 women who underwent C-section and consented to the postplacental insertion of GyneFix PPIUD were enrolled, and 400 completed the 12-month follow-up. Participants were interviewed in the wards after delivery and followed up at 42 days, and months 3, 6, and 12 after delivery. We used Pearl Index (PI) to measure the rate of contraceptive failure, life-table method to measure the rate of PPIUD discontinuation, including IUD expulsion, and Cox regression model to explore the risk factors associated with discontinuation of the device.

Results: Nine pregnancies were detected during the first year after GyneFix PPIUD insertion: seven were due to device expulsion and two occurred with PPIUD *in situ*. The PIs for overall 1-year pregnancy rate and pregnancies with IUD *in situ* were 2.3 (95% CI: 1.1–4.4) and 0.5 (95% CI: 0.1–1.9), respectively. The 6- and 12-month cumulative expulsion rates for PPIUD expulsion were 6.3% and 7.6%, respectively. The overall 1-year continuation rate was 86.6% (95% CI: 83.3–89.8). We did not identify any patient with insertion failure, uterine perforation, pelvic infection, or excess bleeding due to GyneFix PPIUD insertion. Women's age, education, occupation, previous history of C-section, parity, and breastfeeding were not associated with removal of GyneFix PPIUD in the first year of use.

Conclusions: Postplacental insertion of GyneFix PPIUD is effective, safe, and acceptable for women undergoing C-section. Expulsion is the most common reason for GyneFix PPIUD discontinuation and pregnancy.

☆ Conflicts of interest: The authors declare that they have no conflict of interest.

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The expulsion rate for GyneFix PPIUD is lower than that for framed IUDs, but more evidence is needed for a firm verdict.

1. Introduction

A short interpregnancy interval is associated with increased risks of adverse maternal, perinatal, infant, and child outcomes [1–3]. Among women with a previous cesarean section (C-section) delivery, an interval of < 6 months was associated with increased risks of uterine rupture, blood transfusion, and other delivery-related complications [3]. The World Health Organization recommends that women should wait for 24 months after a live birth before attempting the next pregnancy [4]. Nevertheless, approximately 13% of the women had unintended pregnancy within 24 months postpartum in China, and three-quarter of the postpartum unintended pregnancies led to abortion [5,6].

Providing intrauterine devices (IUDs) for contraception during the postpartum period is cost-effective and efficient in preventing unintended pregnancies. Postpartum IUD (PPIUD) insertion does not require significant increase in staff, supervision, or infrastructure requirement [7], can be used as a first-line contraceptive agent for eligible patients [8], and was thus endorsed by the World Health Organization, American College of Obstetricians and Gynecologists, and several other national and international agencies, including USAID, UNFPA, IPPF, Figo, and Chinese Medical Association [7,9,10].

PPIUD can be inserted within 10 min of the placental expulsion. A systematic review showed that the expulsion rates of framed PPIUDs within one year were lower for IUDs placed at the time of cesarean section, as compared with postplacental placement after vaginal delivery [11]. Two more recent studies showed that the expulsion rate of postplacental insertion of framed PPIUDs was relatively high, for example, 38% at 3 months and 8% at 6 months after delivery among TCu380A users, respectively [12,13]. Dr. Wildemeersch, a Belgian gynecologist, thus innovated the frameless GyneFix PPIUD in order to reduce the risk of expulsion [14]. The GyneFix PPIUD consists of a length of nonbiodegradable 0-size monofilament surgical thread with six copper sleeves with a total surface area of 330 mm^2 attached to it. An anchoring knot with a cone-shaped biodegradable body located at the far end of the thread helps the device to be secured in the uterine cavity during and after uterine involution. Before the device insertion, the doctor inspected the uterine cavity to confirm the absence of placental residue, abdominal cavity, and any other contraindication for the use of GyneFix PPIUD after placenta removal. The device was preloaded into the inserter and packed in a peel-pack. The doctor externalized the uterus from the abdominal wall incision and fixed the uterine fundus with her left hand, while holding the inserter to place the GyneFix PPIUD into the uterine fundus through the uterine incision. Then, the left hand was used to feel the inserter being inserted into the uterine fundus. Next, the control button of the inserter handle was pressed with the right hand, and the implant rod was slowly pushed to fix the cone inside the myometrium. The inserter was gently withdrawn from the cavity. The implant rod and outer cannula were withdrawn at the same time. Then, the movable surgical thread could be seen extending from the uterine cavity. The thread was gently pulled to confirm appropriate placement and retention of the device. Then, any end of the movable thread was pulled out of the cavity, leaving the six connected copper tubes inside the uterine cavity. The uterus was closed according to the standard C-section procedure.

GyneFix PPIUD was approved for use in China in 1999, and China is the only country that has approved it for use. However, limited evidence exists in the Chinese and English literature databases regarding the effectiveness, safety, and acceptability of the device. Although several Chinese studies have been performed, almost all have serious limitations, including a small sample size (200 participants or fewer in each arm), reporting the percentage of contraceptive failure rather than the widely used Pearl Index (PI, number of pregnancies per 100 women years [WY] of follow-up), or using the life-table method to estimate the risks of pregnancy and expulsion, and not analyzing the patients with loss to follow-up in data analysis [15–18]. Furthermore, none of the previous studies have been published in international journals. The aims of this study were to assess the effectiveness, expulsion rate, safety, and acceptability of postplacental insertion of GyneFix PPIUD in women undergoing cesarean section using a prospective cohort study design and contributing to the literature on immediate PPIUD placement.

2. Methods

2.1. Study population

We conducted this multicenter prospective cohort study (Trial registration number: ChiCTR1900023828) between January 2018 and November 2020. We enrolled women aged 20–45 years with a singleton live birth delivered by C-section at 14 hospitals in four eastern coastal provinces of China. We excluded patients with thromboembolic disorders, postpartum hemorrhage (defined as > 500 mL), prolonged rupture of membranes (defined as > 24 hours), uterine abnormalities, uterine atony, uterine infection, clinical cervicitis or vaginitis, polyhydramnios, suspicion of uterine fibromyoma, current or previous endometrial or cervical malignancy, any cardiac, renal, and/or hepatic diseases, or any other medical or nonmedical conditions due to which the patients were not suitable for participation in the study.

2.2. Sample size

The primary outcome was pregnancy rate of postplacental insertion of GyneFix PPIUD in women undergoing C-section. According to the European Medicines Agency guidelines, studies of new contraceptive products should include at least 400 women who have completed 1 year of treatment [19]. Assuming 20% of loss to follow-up by the end of the first year of use, at least 500 women should be enrolled to participate in this study.

2.3. Data collection and follow-up

We screened pregnant women who received prenatal care in their third trimester of pregnancy at the study hospitals. The potential participants were counseled and informed regarding the expected postpartum symptoms, benefits, and side effects of GyneFix PPIUD. The C-sections were performed by a doctor trained in GyneFix PPIUD insertion. The doctor inspected the uterine cavity to confirm the absence of placental residue and any other contraindication for the use of GyneFix PPIUD after placenta removal. Clinicians placed the device immediately after placenta expulsion in women who fulfilled the study eligibility criteria. We interviewed participants in the wards before they were discharged from the hospital. Information related to the background characteristics, pregnancy and disease histories, and outcomes was asked and information on GyneFix PPIUD placement was extracted from the

electronic medical records by site investigators. Participants returned to the delivery hospitals 42 days after childbirth, and pelvic ultrasound was performed to determine the presence and position of the device in the uterine cavity. Subsequently, participants were scheduled to be followed up via telephone and WeChat (a popular messaging app) at months 3, 6, and 12 after childbirth to collect information on PPIUD expulsion, removal, and related reasons, adverse events, breastfeeding, and pregnancy if applicable. Participants were asked "Is GyneFix IUD still used?" at each contact. Once the women noticed the device expulsed out of the vagina, they were asked to return to the hospital and had an ultrasound examination to confirm the absence of the device. Furthermore, participants were advised to return to the hospital in case of foul-smelling vaginal discharge different from the usual lochia; feeling of being unwell, fever, or chills; symptoms of pregnancy; or feeling of a foreign body in the vagina. In cases of device expulsion, participants were offered reinsertion if they wanted to continue using the device for contraception, but they were excluded from further analysis. Women who did not want to use IUDs were offered other contraceptive methods.

2.4. Interpretation of key variables

Pregnancy was confirmed using urine human chorionic gonadotropin (hCG) level and B-ultrasound scan. Pregnancy could occur due to IUD expulsion or with IUD *in situ*. We calculated three PIs: overall, PI associated with expulsions, and PI with IUD *in situ*. Women with ongoing lochia discharge for longer than 42 days were considered to have prolonged lochia discharge. Irregular bleeding refers to any bleeding that does not occur during menses. Change in menstrual cycle is defined as a menstrual cycle that is longer or shorter than usual. Excessive uterine bleeding refers to menstrual flow that is much heavier than usual.

2.5. Statistical analysis

We used SAS (version 9.4) for data analysis. We reported pregnancy PI with 95% confidence interval (95% CI) based on Poisson's assumption for time to event. We used the life-table method to estimate the discontinuation/continuation rate of the device during the first year of use. We used Cox proportional hazards model to explore the influence of factors on device discontinuation. We censored participants at the end of the first year if they continued the device, or at the date of their last interview if they discontinued the device, whichever occurred earlier.

3. Results

3.1. Baseline characteristics and GyneFix PPIUD insertion

We screened 510 pregnant women who received prenatal care in their third trimester of pregnancy, intended to have a C-section, and requested a GyneFix PPIUD at the study hospitals. Forty women were excluded because they did not fulfill the eligibility criteria. Consequently, 470 participants were enrolled in this study, and 400 completed the 1-year follow-up. The follow-up rates at day 42, and months 3, 6, and 12 after delivery were 98.5%, 88.7%, 89.4%, and 85.1%, respectively (Fig. 1). Table 1 presents the participant characteristics.

3.2. Pregnancy and expulsion rates

Of the 470 enrolled participants, 463 (98.5%) were followed up at least once after delivery and contributed a total of 388.5 WY of follow-up during the first year of IUD use, including 211.2 WY in the first 6 months and 177.3 WY in the second 6 months, respectively. We detected nine pregnancies during the first year of IUD use, including five in the first half and four in the second-half year (Table 2), leading to an overall 1-year pregnancy PI of 2.3 per 100 WY (95% CI: 1.1–4.4) and the first and second 6-month PIs of 2.4 per 100 WY (95% CI: 0.8–5.5) and 2.3 per 100 WY (95% CI: 0.6–5.8), respectively (Table 3). We identified two pregnancies with the IUD *in situ*, resulting in the 1-year pregnancy rate with IUD *in situ* 0.5 per 100 WY (95% CI: 0.1–1.9). Alternatively, the pregnancy rate due to IUD expulsion was 1.8 per 100 WY (95% CI 0.7–3.7).

Thirty-two (6.9%) expulsions occurred during the first year of IUD use: 10 (2.2%) in the second month and 27 (5.8%) in the first 6 months after IUD insertion. The expulsion rate was significantly higher in the first than in the second 6 months (5.8% vs. 1.1%). The results of life-table analyses show that the cumulative 3-, 6-, and 12-month rates were 0.2%, 1.2%, and 2.4% for pregnancy, and 2.7%, 6.3%, and 7.6% for IUD expulsion, respectively.

3.3. Other safety measurements

The average duration of lochia was 31.2 ± 16.1 days. At 6 weeks, two (0.4%), two (0.4%), and zero patients had endometritis, vaginitis, and pelvic infection, respectively. The most frequent bleeding profile was amenorrhea, which declined from 37.4% at 3 months to 11.2% at 6 months and 3.3% at 12 months after delivery. In addition, 6% to 9% of the participants reported excessive bleeding at the 3-, 6-, and 12-month interviews. Prolonged or shortened menstrual cycles were reported by 3% to 6% of the participants. Irregular bleeding was noted in 2% to 4% of the participants during the first year of use. Furthermore, less than 2% reported lower abdominal pain, prolonged lochia, increased leukorrhea, and abnormal leukorrhea (Table 4). Twelve participants removed IUDs due to above complications, accounting for 2.6% (12/463) of all women followed up. Of them, nine (1.9%) were due to excessive uterine bleeding, two (0.4%) were due to lower abdominal pain, and one (0.2%) was due to increased leukorrhea.

3.4. Discontinuation and continuation rates

In total, 58 participants discontinued GyneFix PPIUD during the first year of use. In addition to the 32 expulsions and nine pregnancies (seven due to IUD expulsions), six participants discontinued due to excessive vaginal bleeding and/or lower abdomen pain, and 18 due to other medical reasons. Of the 32 expulsions, 25 were recognized and confirmed by ultrasound scan, 7 were not recognized and led to unintended pregnancies. The life-table analyses showed that the cumulative 12-month discontinuation rates due to expulsion, excessive bleeding/lower abdominal pain, and other medical reasons were 7.6%, 1.5%, and 4.3%, respectively. No participant removed the device due to nonmedical reasons (Table 5). The cumulative continuation rates of the device rapidly declined to 91.5% (95% CI: 88.9–94.1) at the fourth month after delivery and then declined slowly to 86.6% (95% CI: 83.3–89.8) by the end of the first year of use (Fig. 2).

Results of the Cox regression analysis indicated that women's age, education, occupation, previous history of C-section, parity, and breastfeeding were not associated with removal of GyneFix PPIUD in the first year of use (data not shown).

4. Discussion

4.1. Main findings

In our study, the 1-year pregnancy rate of GyneFix PPIUD was 2.3 per 100 WY (95% CI: 1.1–4.4), and the rates in the first and second 6 months were similar (2.4 per 100 WY vs. 2.3 per 100 WY). These findings are similar to previous Chinese studies, in which 0% to 2.5% of the GyneFix PPIUD users became pregnant during the first year of

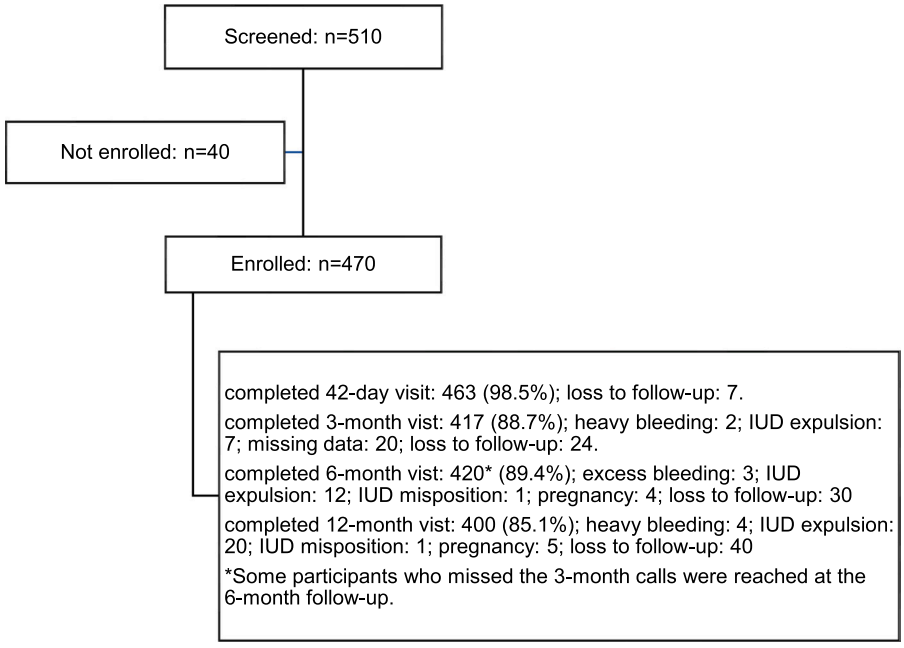

Fig. 1. Participant flow diagram for an observational prospective cohort study on the effectiveness, safety, and acceptability of postplacental insertion of GyneFix postpartum intrauterine device (within 10 min after expulsion of placenta) in women with cesarean delivery in China.

Table 1
Baseline characteristics of participants using GyneFix postpartum intrauterine device in China in 2018 (n = 470)

Characteristics	n	%
Maternal age (y)		
20–24	31	6.6
25–29	141	30.0
30–34	185	39.4
35–39	98	20.9
40–45	15	3.2
Education		
Primary school	20	4.2
Middle school	237	50.4
College	107	22.8
University and above	106	22.6
Occupation		
Blue collar	121	25.7
White collar	81	17.2
Housewife	163	34.7
Others	105	22.3
Parity		
Primipara	58	12.3
Multipara	412	87.7
Number of prior cesarean sections		
0	61	13.0
1	356	75.7
2+	53	11.3
Gestational age (wk)		
24–37	61	13.0
38–42	404	85.9
43	5	1.1
Breastfeeding		
Exclusive breastfeeding	341	72.5
Mixed feeding	67	14.2
Nonbreastfeeding	62	13.3

Table 2
Pregnancies in GyneFix postpartum intrauterine device users during the first year after cesarean section in China during 2018–2019

Case number	Months to fertilization	Age (y)	IUD location
1	3	31	Expulsion
2	4	21	Expulsion
3	4	36	Expulsion
4	4	31	Expulsion
5	5	33	Expulsion
6	8	31	Expulsion
7	10	34	*In situ*
8	10	34	*In situ*
9	12	32	Expulsion

IUD, intrauterine device.

use [15,16,18]. Of the nine pregnancies we detected in the first year postpartum, seven were due to IUD expulsion (1.8 per 100 WY) and two were pregnancies with IUD *in situ* (0.5 per 100 WY). This finding indicates that GyneFix PPIUD is effective for C-section women; however, users should be counseled on the expulsion risk because most pregnancies (7/9) were due to IUD expulsion.

In our study, the 1-year expulsion rate was 6.9%, which is higher than findings of two previous Chinese studies (1.6% and 2.5%, respectively) [17,18]. The expulsion rates of the previous studies might have been underestimated because they did not analyze the patients with loss to follow-up and participants' withdrawal in data analysis. In the present study, the expulsion rate was significantly higher in the first compared with the second 6 months of use (5.8% vs. 1.1%). These results suggest that the IUD users should be informed of the increased risk of expulsion during the first 6 months postpartum.

We did not identify any previous clinical studies of GyneFix PPIUD from outside China. Alternatively, the framed IUDs, for example, TCu380A and LNG-IUD, are the popular PPIUDs in many other countries. Studies from India [8] and Brazil [20] showed that the 1-year cumulative expulsion rates of postplacental insertion of TCu380A were 17.3% and 39.4%, respectively; the 1-year cumulative expulsion rate for LNG-IUD users was 22.2%. Results of a systematic review showed that the expulsion rates were lower for IUDs immediately placed after C-section than after vaginal delivery [11]. The differences in population, service provider, length of follow-up, and mode of delivery may contribute to the variation in expulsion rates between studies.

In our study, none of the patients had uterine perforation or pelvic infection during or after GyneFix PPIUD insertion. Approximately 37%, 11%, and 3% of the participants at the 3-, 6-, and 12-month interviews reported amenorrhea. The high prevalence and decline in amenorrhea might be due to the physiology of lactational amenorrhea, which is

Table 3
Pregnancy Pearl Indices (PI, per 100 WY) of GyneFix postpartum intrauterine device in China during 2018–2019, by months of use

Time segment since delivery (mo)	WY of follow-up	Pregnancy with IUD expulsion			Pregnancy with IUD *in situ*			All pregnancies		
		Events	PI	95% CI	Event	PI	95% CI	Events	PI	95% CI
1–6	211.2	5	2.4	0.8–5.5	0	0.0	0.0–1.8	5	2.4	0.8–5.5
7–12	177.3	2	1.1	0.1–4.1	2	1.1	0.1–4.1	4	2.3	0.6–5.8
1–12	388.5	7	1.8	0.7–3.7	2	0.5	0.1–1.9	9	2.3	1.1–4.4

IUD, intrauterine device; WY, women years.

Table 4
Percentage distribution of adverse events in GyneFix postpartum intrauterine device users at months 3, 6, and 12 after childbirth in China during 2018–2019

Adverse events	3 mo (N = 417)	6 mo (N = 420)	12 mo (N = 400)
Amenorrhea	37.4	11.2	3.3
Excessive uterine bleeding	6.2	9.1	8.3
Changes in menstrual cycle	3.1	5.7	5.0
Irregular bleeding	3.1	1.9	3.5
Lower abdominal pain	2.2	1.7	1.5
Prolonged lochia	1.9	0	0
Increased leukorrhea	1.2	1.4	1.0
Abnormal leukorrhea (color, smell)	0	1.0	0.5

associated with the frequency and duration of lactation. The prevalence of other adverse events, including changes in menstrual cycle, irregular menstrual bleeding, lower abdominal pain, increased leukorrhea, and prolonged lochia, was low. The evidence presented in this study demonstrates that postplacental insertion of GyneFix PPIUD is generally safe for women after C-section delivery.

The overall 1-year discontinuation rate was 13.4% and expulsion accounted for almost 60% of the cases. Similar to other types of PPIUDs, expulsion is a major problem. However, IUD expulsion itself does not constitute a serious harm if it is recognized in a timely manner. Women should be counseled regarding the signs of expulsion and ultrasound should be performed once they have the feeling of a foreign body in the vagina in order to mitigate the risk of unrecognized expulsion and unintended pregnancy. Despite the problems of expulsion and side effects, the overall 1-year continuation rate was 86.6%, indicating the acceptability of GyneFix PPIUD in women after C-section.

This is the first prospective cohort study published in English regarding the effectiveness and safety of GyneFix PPIUD. Our sample size is larger than that of previously published studies. The study manifests several limitations. It is a single-arm prospective observational study rather than a randomized controlled clinical trial. We followed up participants via phone calls or WeChat, which may have led to the underreporting of the side effects of the device. We did not consider the effects of breastfeeding and frequency of coitus on the effectiveness of GyneFix PPIUD.

Table 5
3-, 6-, and 12-month cumulative discontinuation rates of GyneFix postpartum intrauterine device in women undergoing cesarean section, by reasons of discontinuation in China during 2018–2019 (life-table analysis, N = 463)

Reasons of discontinuation	3 mo		6 mo		12 mo	
	Cumulative rate since delivery (n)	95% CI	Cumulative rate since delivery (n)	95% CI	Cumulative rate since delivery (n)	95% CI
Expulsion[a]	2.7 (12)	1.2–4.2	6.3 (27)	3.9–8.6	7.6 (32)	4.8–10.5
Excess bleeding and/or abdominal pain	0.5 (2)	0–1.1	0.9 (4)	0–1.9	1.5 (6)	0.2–2.8
Other medical reasons[b]	0.9 (4)	0.0–1.8	4.0 (17)	2.1–6.0	4.3 (18)	2.2–6.53
Overall discontinuation[c]	4.0 (18)	2.2–5.8	11.1 (49)	8.0–14.2	13.4 (58)	9.8–17.1

[a] Including expulsions leading to pregnancy.
[b] Including reproductive tract infection, pelvic infection, uterine perforation, misplaced intrauterine device, and intrauterine device partial expulsion.
[c] Including discontinuations due to pregnancy.

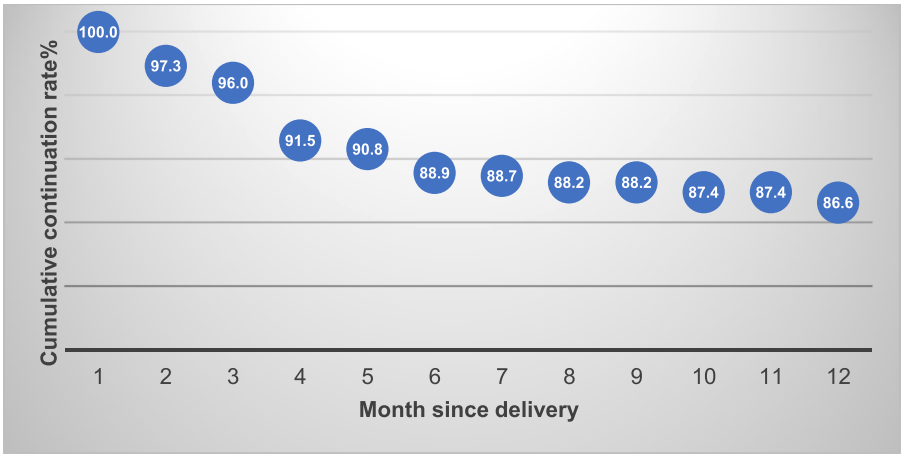

Fig. 2. Cumulative continuation rate of GyneFix postpartum intrauterine device in women undergoing cesarean section during the first 12 mo after delivery.

GyneFix PPIUD is a safe and effective postpartum contraceptive method after C-section. Expulsion is the most common reason for GyneFix PPIUD discontinuation and pregnancy. The expulsion rate for GyneFix PPIUD is lower than that for framed IUDs, but more evidence is needed for a firm verdict.

Authors' contributions

Y.C. developed the concept, supervised the data collection, analyzed the data, wrote the first paper draft, interpreted the results, and reviewed the final version. G.F.H., H.P.Z., H.Y., S.J.L., T.G., W.H.Y., C.H.S., W.J.R., Y.Q.X., B.M.Y., T.T.C., Y.J.G., and Y.Z. collected the data and reviewed the paper; Y.Z. analyzed and interpreted the data, and revised the paper. L.N.C. collaborated in the study design, reviewed, and revised the paper. All authors revised and approved the final paper draft.

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