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ORIGINAL ARTICLE ***Fertility control***

Effect of vaginal administration of misoprostol before intrauterine contraceptive insertion following previous insertion failure: a double blind RCT

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STUDY QUESTION: Is pretreatment with misoprostol useful in insertion of intrauterine contraceptives (IUCs) after insertion failure at the first attempt?

SUMMARY ANSWER: Pretreatment with intravaginal administration of 200 mcg of misoprostol after IUC insertion failure 10 and 4 h before the second attempt of IUC placement was significantly better than placebo at facilitating the insertion of an IUC.

WHAT IS KNOWN ALREADY: One of the reasons for low use of IUCs is the concept that insertion is difficult. Misoprostol was used in several randomized clinical trials (RCT) before IUC insertion to facilitate the insertion. In general, the results showed no significant differences when compared with placebo. However, most previous studies have been carried out among unselected women whereas the present study is among women with previous insertion failure.

STUDY DESIGN, SIZE, DURATION: This was a double blind RCT conducted between February 2013 and October 2014. Participants were 104 women who requested an insertion of an IUC and the insertion failed at the first attempt. After insertion failure, the women received a sealed envelope with misoprostol or placebo. The randomization system (1: 1) in one block size was computer-generated.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study was conducted at a tertiary care centre. The women were instructed to insert vaginally one tablet of misoprostol 200 μg (Prostokos, Hebron, Cariacica, PE, Brazil) or placebo 10 and 4 h before the woman returned to the clinic for a new insertion attempt. The outcomes were successful IUC insertion and the use of a cervical dilator immediately prior to the insertion procedure.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 2639 women requested the insertion of an IUC during the study period. The IUC was inserted at the first attempt in 2535 women (96%) and 104 women in whom we were unable to insert the device were eligible to participate in the RCT. Four women declined and 100 women were randomized (55 for the misoprostol group and 45 for the placebo group). From the 100 participating women, the levonorgestrel-releasing intrauterine system (LNG-IUS) was chosen by 55 and 37 women and the TCu380A intrauterine device (Cu-IUD) was chosen by none and 8 women in the misoprostol and placebo group, respectively. Seven and three women allocated to misoprostol and placebo, respectively, never returned to the clinic after randomization. We placed the IUC in 42 (87.5%) out of the 48 women and in 26 (61.9%) out of the 42 women randomized to misoprostol and placebo, respectively ($P = 0.0066$). Regarding the Evaluable Population the relative risk (RR) of successful insertions was 1.41 (95% confidence interval (CI) for absolute difference (8.2, 43.0), $P = 0.0066$); in the Intent-to-Treat Population the RR (95% CI) was 1.32 (0.3, 36.9). Multiple regression analysis showed that the significant variables associated with the insertion failure were the number of Caesarean section ≥ 1 ($P = 0.020$) and the use of placebo ($P = 0.026$). Dilators were used in 21 (43.7%) out of the 48 and 21 (50%) out of the 42 women randomized to misoprostol and placebo, respectively ($P = 0.804$).

LIMITATIONS, REASONS FOR CAUTION: The limitations were that the majority of the women chose the LNG-IUS, and consequently the data for the Cu-IUD were limited, and there was a small number of nulligravidas.

WIDER IMPLICATIONS OF THE FINDINGS: The results show that IUC insertion difficulties and failures are not common. Pretreatment with intravaginal misoprostol facilitated IUC insertion after failure of insertion at the first attempt, and insertion failure was associated with number of Caesarean sections.

STUDY FUNDING/COMPETING INTEREST(S): This study received partial financial support from the *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP), grant # 2012/10085-0, and from the National Research Council (CNPq), grant #573747/2008-3. All the TCu380A IUDs were donated by Injeflex, São Paulo, Brazil, and all the LNG-IUS were donated by the International Contraceptive Access Foundation (ICA), Turku, Finland. Both donations were provided in the form of unrestricted grants. The authors declare that there are no conflicts of interest associated with this study.

TRIAL REGISTRATION NUMBER: ClinicalTrial.gov NCT01754649.

Key words: misoprostol / insertion failure / intrauterine contraceptives / copper intrauterine device / levonorgestrel-releasing intrauterine system

Introduction

Intrauterine contraceptives (IUCs) are one of the reversible contraceptives with a highest contraceptive effectiveness (Winner *et al.*, 2012; Bahamondes *et al.*, 2014a; Ferreira *et al.*, 2014). The common models in use worldwide, except for China, are the TCu380A intrauterine device (Cu-IUD) and the levonorgestrel-releasing intrauterine system (LNG-IUS) (ESHRE Capri, 2008). The main reasons associated with a low IUC use are high cost in some settings and fear of pain at insertion by women. For healthcare professionals (HCPs) the obstacles to use include lack of training in insertion, fear of causing pain with the procedure and difficulties during the procedure that could end in failure of insertion (Bahamondes *et al.*, 2011; Marions *et al.*, 2011). Many HCPs believe that failure or difficulty of insertion is common in adolescents and nulligravidas and this is one of the reasons that restrict IUC use, despite the evidence and recommendations supporting use in these groups (Berenson *et al.*, 2013).

In many studies, misoprostol, administered before the insertion of an IUC, was used with the aim of priming the internal cervical os in order to improve the ease of insertion or to reduce the rate of insertion failure (Heikinheimo *et al.*, 2010; Schaefer *et al.*, 2010; Dijkhuizen *et al.*, 2011; Edelman *et al.*, 2011). Although misoprostol was administered at different doses and by different routes, no significant differences were observed when compared with placebo in RCTs (Heikinheimo *et al.*, 2010; Edelman *et al.*, 2011). However, one RCT (Scavuzzi *et al.*, 2013) compared misoprostol 400 μg and placebo administered vaginally 4 h prior to the insertion of a TCu380A IUD and showed an increase in the ease of insertion and pain reduction at insertion with misoprostol; but an increase of cramps was observed.

Despite the evidence that misoprostol is not useful prior to IUC insertion, in a US-based survey (Ward *et al.*, 2011), the authors evaluated 2211 responses from a survey in which they assessed whether HCPs routinely used misoprostol to facilitate IUC insertion in nulliparous women. Of the respondents, 49.7% reported that they used misoprostol and 40% of the misoprostol users responded that they did so purely based on their experience with all IUD insertions among nulliparous women.

Based on the previous studies, we considered that it is necessary to conduct further studies to contribute to this debate. Consequently, we conducted an RCT with the objective to evaluate if pretreatment with misoprostol is useful in insertion of IUC after insertion failure at the first attempt.

Materials and Methods

This was a double blind RCT conducted at the Family Planning clinic, Department of Obstetrics and Gynaecology, University of Campinas (UNICAMP) Medical School, Campinas, SP, Brazil. The Ethical Committee approved the study and all the women signed an informed consent before entering the study. The study was conducted between February 2013 and October 2014 and it was registered on ClinicalTrial.gov under the number NCT01754649.

Women who came to the clinic and requested an insertion of either a TCu380A IUD (Optima®, Injeflex, São Paulo, Brazil) or an LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) were eligible to participate. Women with insertion failure at the first attempt were invited to participate. We considered IUC insertion a failure if we were unable to pass the internal cervical os with the uterine sound, metallic dilator number 3 and an Os Finder (Bioteque America, Inc., Fremont, CA, USA), which is a tapered plastic dilator with a 1.75 mm tip to 3.8 mm outer diameter. When any of the HCP at the clinic failed to insert the IUC, they called one of the authors (two physicians and one nurse highly experienced in IUC insertion) who tried the IUC insertion again for the first attempt and these three HCPs were the same who tried the insertion again at the second attempt.

The invited women signed an informed consent form and received a sealed opaque envelope with the medication or placebo. The randomization system was performed by the pharmaceutical company which manufactured the misoprostol and placebo tablets (Prostokos, Hebron, Cariacica, PE, Brazil), using a SAS computer-generated system (in one block) to allocate the women to the misoprostol or placebo group (1:1). The sealed envelope with the codes was stored outside the research centre. The pharmaceutical company prepared the placebo tablets to be identical in shape, colour and weight to the active drug tablets and they sent the material in sealed envelopes identified only by a sequential number. The women were instructed to insert vaginally one tablet of misoprostol 200 μg or placebo 10 and 4 h before the woman returning to the clinic for the second attempt of insertion. The outcomes were the successful insertion of the IUC and the use of a cervical dilator immediately prior to IUC insertion to facilitate the procedure.

Statistical analysis

Estimated sample size was 92 women (46 per group) based on an assumed proportion of successful insertions of 0.95 in the misoprostol and 0.75 in the placebo group, with a significance of 0.05 and power of 80%. We also estimated the sample size after the increase of the absolute difference between the groups at 21.5% instead of 20% and the sample size was 82 women (41 per group). The women's sociodemographic characteristics were presented as means and standard deviation (SD) and were compared using the Mann–Whitney, Yates χ^2 and Fisher exact tests when appropriate. Also we performed an

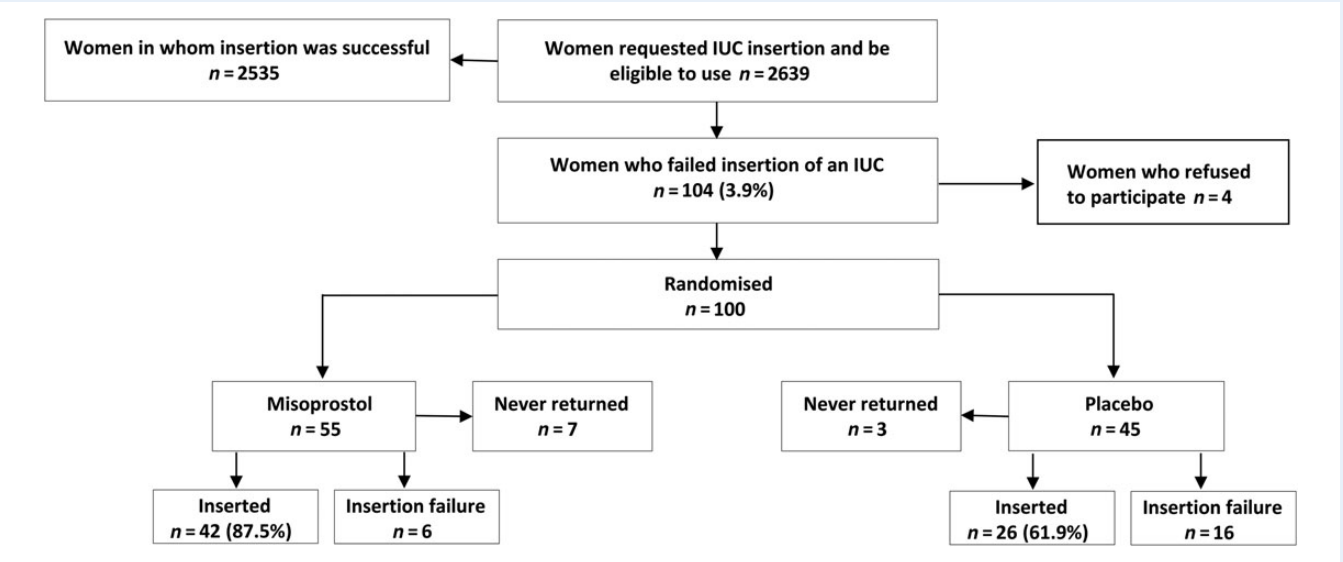

Figure 1 Flow chart of the women who participated in the RCT comparing the effect of vaginal misoprostol before intrauterine contraceptive (IUC) insertion following previous insertion failure with placebo.

Table I Selected characteristics of the women who inserted an intrauterine contraceptive (IUC) at the first attempt and those who participated in the RCT.

Characteristics	Women who received an IUC at the first attempt ($n = 2535$)	Women with insertion failure ($n = 100$)	Women randomized to misoprostol ($n = 55$)	Women randomized to placebo ($n = 45$)
Age (years)[a]	33.7 ± 7.4	36.5 ± 7.0	37.0 ± 7.1	36.4 ± 6.9
Number of pregnancies[b]	1.8 ± 1.1	1.5 ± 1.0	1.6 ± 1.0	1.3 ± 0.9
Number of deliveries[c]	1.6 ± 1.0	1.3 ± 0.9	1.4 ± 1.0	1.2 ± 0.9
Number of Caesarean sections[d]	0.9 ± 0.9	1.1 ± 0.9	1.2 ± 0.9	1.0 ± 0.9
Cu-IUD (*n*)[e]	434	7	0	7
LNG-IUS (*n*)	2101	92	55	37
Use of dilators (*n*)	6	42	21	21
Uterus position (*n*)[f]				
AVF	1945	69	37	32
RVF	398	24	15	9
MV	149	3	1	2
Uterine sounding (cm)[g]	9.2 ± 9.5	7.7 ± 1.0	7.7 ± 1.1	7.8 ± 1.0
Inserted or tried to insert by[h]				
Physician	664	42	31	30
Resident in training	1305	23		
Nurse	428	25	17	12
Medical student	60	2		

All values are mean ± SD.
Cu-IUD: copper-intrauterine device; LNG-IUS: levonorgestrel-releasing intrauterine system; N.S: not-significant.
Missing values for: a: 12 cases; b: 4; c: 2; d: 6; e: 1; f: 47; g: 65; h: 86 cases.
AVF: anteverted uterus; RVF: retroverted uterus; MV: intermediate.

analysis with two defined groups: (i) Evaluable Population; referring to all subjects in the Intent-to-Treat Population who returned to the clinic for the second attempt of IUC insertion; and (ii) Intent-to-Treat Population (ITT); referring to all subjects who were enrolled and received study medication at that visit. We also performed a multiple regression analysis (Poisson model) with the dependent variable: insertion failure (Yes/No) and the independent variables: Group (Misoprostol/placebo); Age: (years); Number of deliveries (0/≥1); Number of Caesarean section (0/≥1); Uterus position: (anteverted, retroverted, intermediate.); Uterine sound (cm); Professional who inserted or tried to do (Physician/Nurse). Significance was established at $P < 0.05$. The data were analysed using SAS/STAT version 9.2; 2011 (Cary, NC, USA).

Results

A total of 2639 women came to the clinic requesting the insertion of an IUC during the period of the study. Figure 1 shows the total sample of women, the allocation and the results of the trial. The sociodemographic details of the acceptors of the IUCs as well as the information of the women who participated in the RCT are presented in Table I. Among the group of women in whom the IUC insertion was successful at the first attempt, 2101 and 434 received an LNG-IUS or TCu380A IUD, respectively. From the 100 randomized women, 55 and 45 were allocated to the group that received misoprostol and placebo, respectively. Seven and three women allocated to the misoprostol and placebo group, respectively never returned to the clinic after randomization. We were able to insert the IUC in 42 (87.5%) out of the 48 women randomized to misoprostol and in 26 (61.9%) out of 42 women randomized to placebo. Regarding the Evaluable Population the relative risk (RR) of successful insertions was 1.41 (95% confidence interval (CI) for absolute difference (8.2, 43.0), $P = 0.0066$); in the Intent-to-Treat Population the RR (95% CI) was 1.32 (0.3, 36.9). Furthermore, we needed to use dilators in 21 (43.7%) out of the 48 and 21 (50%) out of the 42 women randomized to misoprostol and placebo, respectively ($P = 0.804$). Of the 100 women who participated in the RCT, the LNG-IUS was chosen by 55 and 37 women and the TCu380A IUD was chosen by none and 8 women in the group of misoprostol and placebo, respectively.

Table II shows the similar characteristics of the women with IUC insertion failure after misoprostol or placebo use. The multiple regression analysis (Poisson model) showed that the significant variables associated with the failure of insertion were the number of Caesarean sections ≥1 ($P = 0.020$) and placebo use ($P = 0.026$). Five women who received misoprostol complained of gastrointestinal side effects or chills and six women reported mild cramping pain. Painkillers were not given to the participants (Table III).

Table II Selected characteristics of the women with insertion failure of IUC after use of misoprostol or placebo.

Characteristics	Women with insertion failure after use of misoprostol ($n = 6$)	Women with insertion failure after use of placebo ($n = 16$)
Age (years)* (range)	34.2 ± 5.2 (20–45)	35.3 ± 6.0 (20–47)
Number of pregnancies		
0	4	7
1	1	2
2	1	7
Number of Caesarean sections		
None	3	9
1	1	3
2	2	4
Uterus position (n)		
AVF	3	12
RVF	2	3
MV	1	1

*Mean ± SD.

Table III Variables associated with the failure of insertion of IUC according to multiple regression analysis (Poisson model).

Variable	Prevalence ratio	95% confidence interval	*P*-value
Previous Caesarean section (≥1)	0.36	0.16–0.85	0.020
Group (placebo)	2.90	1.13–7.42	0.026

Dependent variable: insertion failure (yes/no); Independent variables: Group (Misoprostol/placebo); Age: (years); Number of deliveries (0/≥1); Number of Caesarean (0/≥1); Uterus position: (AVF/RVF, MV); Uterine sound measure (cm); Professional who inserted or tried to do (Physician/Nurse).

Discussion

Our results showed that misoprostol was significantly better than placebo at facilitating the insertion of an IUC after insertion failed at the first attempt although the use of cervical dilators was similar among both groups. Caesarean section was associated with IUC insertion failure. Previous Caesarean section could be a risk factor for IUC insertion failure because a scar close to the internal os may impair cervical softening or ripening by misoprostol (Ofili-Yebovi *et al.*, 2008). Even though a history of Caesarean section in women without previous labour could be a potential difficulty for IUC placement it is not a contraindication or obstacle to IUC insertion (Bahamondes *et al.*, 2011).

Our results were in the opposite direction with some studies that found that misoprostol was not useful to facilitate the insertion of IUCs. However, most of these previous studies have been carried out with unselected women whereas in the present study women were selected among those with previous insertion failure (Heikinheimo *et al.*, 2010; Ibrahim and Sayed Ahmed, 2013; Lathrop *et al.*, 2013; Espey *et al.*, 2014).

According to our results, only about 4% of the IUC insertions failed at the first attempt and consequently, if we randomized the women before the attempt was made to insert the IUC, the result could be that misoprostol might or might not be useful. This was the situation with the studies that randomized the women before the first attempt of insertion

(Heikinheimo *et al.*, 2010; Edelman *et al.*, 2011; Ibrahim and Sayed Ahmed, 2013; Lathrop *et al.*, 2013; Scavuzzi *et al.*, 2013; Espey *et al.*, 2014). Also, misoprostol was administered by different routes, and in different doses and times of administration before the insertion of the IUC, which jeopardized comparison (Li *et al.*, 2005; Saav *et al.*, 2007; Dijkhuizen *et al.*, 2011). One of the studies that used a similar strategy to our report was a case series with eight women in whom IUC insertion failed at the first attempt due to cervical stenosis. The authors administered misoprostol vaginally at a dose of 400 μg 24 h before the second attempt of insertion and they reported that all the insertions were successful (Li *et al.*, 2005); however, they did not control with placebo.

One of the limitations to the use of IUCs is the belief that many women and HCPs have that the insertion procedure is difficult and likely to provoke pain. Since none of the pain control approaches were efficacious (Gemzell-Danielsson *et al.*, 2013; Bahamondes *et al.*, 2014b), HCPs want to facilitate difficult insertions and reduce the probability of failures, which is already low even in nulliparous women. However, IUC insertion is generally a simple procedure and the need for cervical dilatation or insertion failure is only observed in as small number of women including nulligravidas (Bahamondes *et al.*, 2011). Misoprostol has been tested extensively to facilitate IUC insertion; and although the results are in general ineffectual, many HCPs continue using this drug in routine IUC insertions (Ward *et al.*, 2011). Our results support that misoprostol should be used only after failed insertions.

Our study presents strengths and limitations. One of the limitations was that the majority of the women chose the LNG-IUS as their contraceptive method and consequently the data are limited for the TCu380A IUD. Furthermore, the number of nulligravidas was only 240 (9.5%), 9 (16.4%) and 10 (22.2%) among the entire group of women and those allocated to misoprostol and placebo, respectively. The strengths of the study were the design of a double blind RCT with standardized dosing and route of administration, the strict criteria followed for enrolling the participants and the use of misoprostol only in women in whom the IUC placement failed at the first attempt.

In conclusion, our findings show that the use of misoprostol before IUC insertion after failure of insertion at the first attempt is significantly better than placebo. Our study contributes to increasing the evidence for the usefulness of misoprostol before IUC insertion. Misoprostol is beneficial for cervical priming for IUC placement only for certain groups of women. Our results also show that insertion difficulties and failures are not common.

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All the TCu380A IUDs have been donated by Injeflex, São Paulo, Brazil, and all the LNG-IUS have been donated by the International Contraceptive Access Foundation (ICA), Turku, Finland. In both cases the devices were provided in the form of unrestricted grants.

Authors' roles

M.V.B., X.E.-A. and L.B. conceived the study and were responsible for developing the protocol, inserting all the IUCs after failure, analysing and interpreting the data, and for writing and revising the final version of the manuscript.

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Conflict of interest

The authors declare that there are no conflicts of interest associated with this study.

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