The Carevix™ Device: Assessing pain and effectiveness of a suction-based cervical stabilizer for IUD insertions in the clinic setting: a randomized, controlled (CARE) trial

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Abbreviations

AE	Adverse Event
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
PI	Principal Investigator
PHI	Personal Health Information
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
US	United States
IUD	Intrauterine Device
EMB	Endometrial Biopsy
FDA	Food and Drug Administration

1.0 Background & Rationale

IUD insertions can be painful. Pain at IUD insertion is experienced in a wide range, with some patients feeling little to no pain and others feeling excruciating pain. Fear of IUD insertion pain and pre-procedure anxiety has been shown to cause a higher level of pain during the procedure.[1] In August 2024, the CDC released a statement encouraging a person-centered plan for pain management during IUD insertions and that all patients should be counseled on potential pain as well as the risks, benefits and alternatives for different pain management options.[2] Of note, there is no study other than the 2023 Aspivix European trial on this device, that emphasizes pain specifically at cervical grasp during IUD insertions.[3] Additionally, studies are beginning to assess the role cultural and background characteristics of patients play into the pain experience. One 2020 study showed that race was the only covariate that significantly predicted anticipated pain at IUD insertion and that women with anticipated pain scores above the median had significantly higher perceived pain during all timepoints of the IUD insertion procedure.[4] One study in 2018 tried to assess racial differences in attitude towards IUDs and found that knowledge about IUDs did not differ based on race but Black women were more likely to perceive that they had less knowledge about IUDs compared to white women.[5] Pain as a barrier to IUD uptake has been studied and the results are mixed. One study in 2016 found women who initiated other contraceptives (i.e. oral birth control, injectables, implant, patch, etc.) did not anticipate more pain with IUD insertion than those who initiated IUD[6], but a more recent study in 2024 found fear of pain related to the insertion process as one of the most significant barriers to the use of the IUD. This review of 14 studies in total, found that most looked only at pharmacological methods for pain management with IUD insertion, highlighting a need for more research on non-pharmacological methods to improve patient experience and reduce associated fears.[7]

When IUD insertions are performed, often the cervix needs to be stabilized to facilitate intrauterine entry. The standard approach for cervical stabilization is an invasive, sharp instrument called a tenaculum. This leaves two punctures on the cervix, which can be painful and bleed, which can prolong an IUD insertion procedure. Aspivix ™ has created a **suction-based atraumatic cervical stabilizer** for use with such intrauterine procedures. The First-in-Woman study (RCT with 100 patients) completed in 2 renowned University Hospitals in Switzerland showed positive results in both pain reduction and bleeding (pain reduced by up to 73% and bleeding occurrence reduced by 78%). This new device is **fully FDA approved in January 2023**.

Attached are the company's clinical brochure showing the device, explaining how it is used, and data on effectiveness. In addition, this is the RCT publication on the journal *Contraception* on this device, showing the data cited above.[3]
https://www.contraceptionjournal.org/article/S0010-7824(23)00066-5/fulltext

In 2023, Aspivix ™ launched the AMBASSADOR PROGRAM, a 3–6-month program with free of charge devices for selected hospitals /clinics willing to test extensively Carevix™ in multiple transcervical procedures.

During this time, the Coleman Clinic at Indiana University performed the first trial in the United States utilizing this device on intrauterine procedures at a single site (between 11/2023 to 5/2024) as an expansion of the 2023 European trial. This pilot study involved 60 total patients – 30 patients received tenaculum and 30 received Carevix™. In this study, we expanded to include not only IUD insertions, but also endometrial biopsies and saline infusion sonograms. We also collected some demographic data, including age, relationship status, education level, current work status, and pregnancy history. We did not collect ethnicity or additional cultural identification that may play a role in reproductive decision making, nor did we collect any prior pregnancy prevention strategies the patient had used, why they no longer want to use those options and why they elected for an IUD nor any barriers perceived or anticipated for device removal.

As stated by the recently updated recommendations by the CDC on 8/8/2024 regarding pain management for IUD insertions (attachment, beginning on page 13), pain and fear of pain during IUD insertions can be a barrier to this highly effective, long-acting form of reversible contraception. The CDC also encourages a person-centered plan for IUD placement and pain management during IUD insertions, which should include non-pharmacological choices. As stated in the new CDC recommendations: “barriers to IUD use include patient concerns about anticipated pain with placement and provider concerns about ease of placement, especially among nulliparous patients.” This trial directly addresses this CDC call by seeking to expand non-pharmacological options available to patients to potentially decrease pain during IUD insertions by studying the new suction-based cervical stabilizer, which has only recently begun use in the United States. As stated in the European trial, the Carevix™ device has the potential to decrease pain experienced by the patient, decrease bleeding and therefore potentially time spent during the procedure for both the provider and the patient, and had no difference in visibility by the provider. This is very timely with the new CDC recommendations and an IUD insertion-focused randomized trial to study this device on patients in the United States is needed.

The population this study will focus on is a generally urban-based population but of a large variety of economic, ethnic, social and age- and education-based background. This population is generally of reproductive age, but ranges between 18 and 50. Most identify as female. IU Health-based clinics accept all private and Medicaid-based insurances and include patients with no insurance and this patient population will reflect that variety. Generally, most patients in this study will live and work within the state of Indiana, which also has a near-total abortion ban. In addition, the European data found nulliparous women had much less pain with Carevix™ compared to tenaculum than multiparous women did. We seek to determine if a similar finding is noted in our

population as well as other demographic data that can further align better person-centered contraceptive choices and counseling surrounding pain management for IUD insertion.

2.0 Objective(s)

2.1 Primary Objective

2.1.1 Primary Objective: to assess and compare patient-reported pain during IUD insertion between the Carevix device and tenaculum. Our hypothesis is that patient-reported pain scores comparing Carevix™ to tenaculum **will be lower.** We will assess **pain,** and **predictors for pain scores** including nulliparous vs multiparous, when highest pain scores are reported, and expectation of pain for the procedure.

2.2 Secondary Objective

Secondary Objectives: We will assess **Usability** (provider assessment of ease of use, number of device placement attempts to secure sufficient traction on uterus), **efficacy** (ability to insert IUD with Carevix™ device alone without recourse to conventional tenaculum or other instruments), provider reported bleeding (cervical bleeding and ecchymosis), **overall provider satisfaction**, **patient-reported pain scores** at device placement prior to IUD insertion procedure and after completion of IUD insertion using Visual Analog Scale (VAS), **overall patient satisfaction,** and **overall provider satisfaction.** We aim to expand our pilot trial data collection to assess **cultural background, ethnicity and demographics** while also **assessing prior contraceptive choices, reasons for discontinuation of prior choices** and **reasons for current selection of IUD** insertion and any anticipated **barriers for removal**.

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measures

3.1.1 Primary outcome measures: To assess patient-reported pain, a questionnaire (Attachment #2) will be done after completing the procedure. This takes on average 1-2 minute to complete.

3.2 Secondary Outcome Measures

3.2.1 Secondary outcome measures: To assess provider-reported ease of use and provider satisfaction with the device, the provider will complete a questionnaire following the patient's completion of their portion of the questionnaire (Attachment #3). This takes on average 1-2 minutes to complete. To assess cultural background, ethnicity and

demographics while also assessing prior contraceptive choices and reasons for current selection of IUD insertion, these questions will be answered in same survey as primary outcome measure after completing the procedure.

4.0 Eligibility Criteria

4.1 Inclusion Criteria (to be assessed prior to procedure)

- Age 18 years or older
- Able to consent on their own
- Scheduled and will undergo an IUD insertion within 90 days of consent
- Planned use of cervical stabilization device for placement
- Procedure being performed by a trained provider
- Provider is willing to use Carevix™ for scheduled procedure

4.2 Exclusion Criteria (to be assessed by provider at time of procedure)

- Vaginal bleeding of unknown origin
- Cervix less than 26 mm in diameter
- Nabothian cyst on anterior lip of cervix
- Cervical myomas
- Cervical abnormalities/shape
- Pregnant
- Participants who are not fluent in and/or do not fully understand, read, write, or speak the English language
- Other inability to provide informed consent to participate
- Initial attempt to place the IUD without any cervical stabilization

4.3 Other Criteria

4.3.1 If the patient does not require ANY cervical stabilization after consent, the subject status will be considered **ineligible for device placement** and will be excluded. These patients will be replaced by another eligible recruit.

4.3.2 This trial will be conducted with intention-to-treat analysis. If a patient is randomized into the Carevix™ arm and Carevix™ is attempted but the procedure is unable to be completed

with the Carevix™ and instead a tenaculum is required, their data will be analyzed in the Carevix™ arm. An exploratory "as treated" analysis may be performed if >15% of patients get an intervention not originally randomized.

5.0 Study Design

Indiana University Health clinics will perform a randomized trial on Carevix™ vs tenaculum for IUD insertions. All patients presenting for IUD insertion who fit inclusion criteria will be approached with this study. Upon consent and review of the study information sheet (attached), they will be randomized to receive either the Carevix™ device or the tenaculum. The patient will be consented for the IUD insertion as per normal clinic protocol and for the study as per study protocol.

Randomization will occur by block randomization to ensure that equal numbers are allocated to each group. To accomplish this, study staff will utilize a random number generator to assign interventions, blocked in groups of 6. In order to account for potentially pivotal differences, we will stratify randomization on two characteristics, randomizing nulliparous and parous patients separately, as well as individual clinic. All assignments then being put into sealed, opaque, sequentially numbered envelopes to be chosen by study staff after the participant has consented to the study. Once the envelope is chosen the patient and provider will be made aware of which arm the participant is allocated. Due to the nature of the devices, participants and care providers are unable to be blinded for this study.

Baseline characteristics and demographics will be collected on all participants enrolled, flow of participants through study using CONSORT diagram, number and reasons participants not randomized, and comparison between those randomized and those not randomized. All participants randomized reported according to Intention-to-Treat (ITT) principle. Number and reasons for switching from Carevix™ to the standard cervical traction device (tenaculum), or the converse, will be reported. Device efficacy and usability outcomes, and participant pain assessments and outcomes to be compared by randomized arm, and within Carevix™ arm according to actual method used.

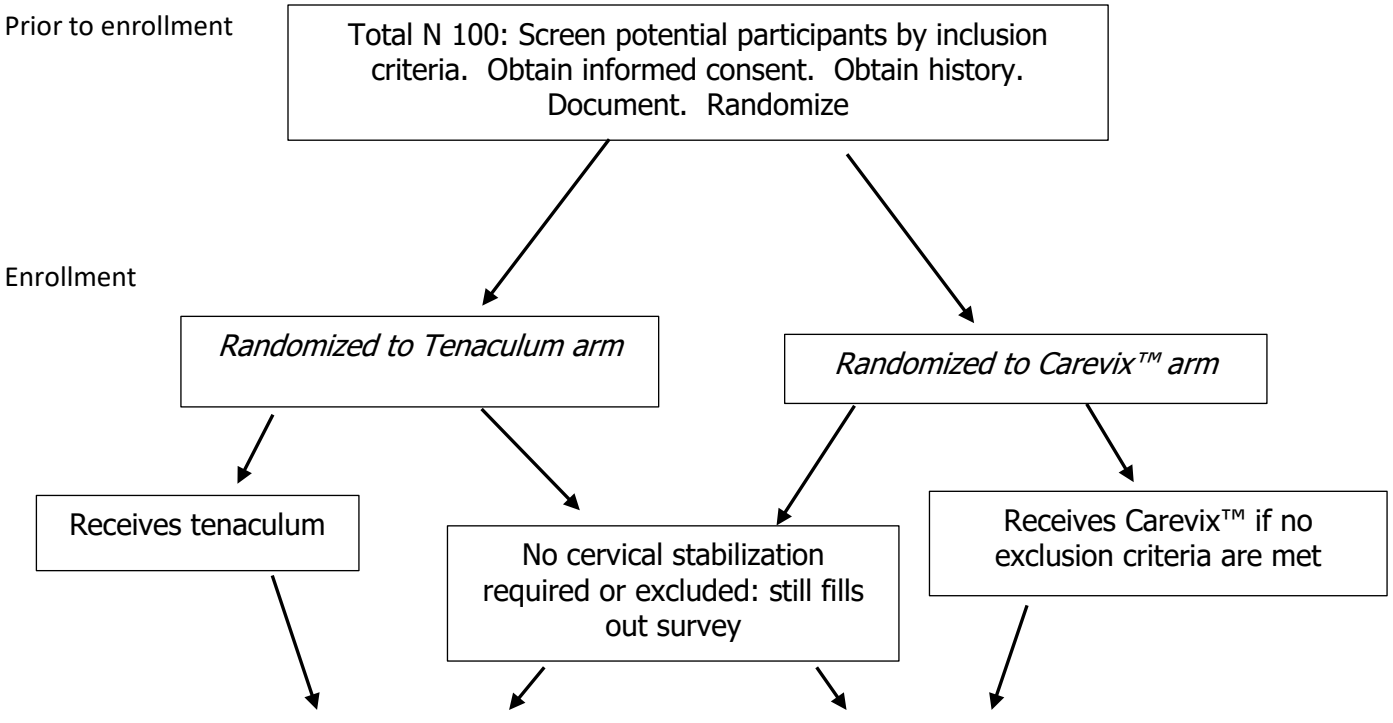
Power analysis: For our analysis, we used the Wilcoxon test instead of the t-test because we anticipate that the data will not be normally distributed, based on the results of our pilot study. Since the Wilcoxon test does not rely on the normality assumption, we used a simulation approach to estimate the power rather than the t-test power analysis. In the pilot trial dataset, we found a 1.64-point difference in pain scores from the mean difference for two groups with the parameters mean = 1.26 and sd = 1.28 for the Carevix group and mean = 2.9 and sd = 2.88 for the Tenaculum group, but only had 44% power in that pilot sample. Assuming a similar pain score difference,

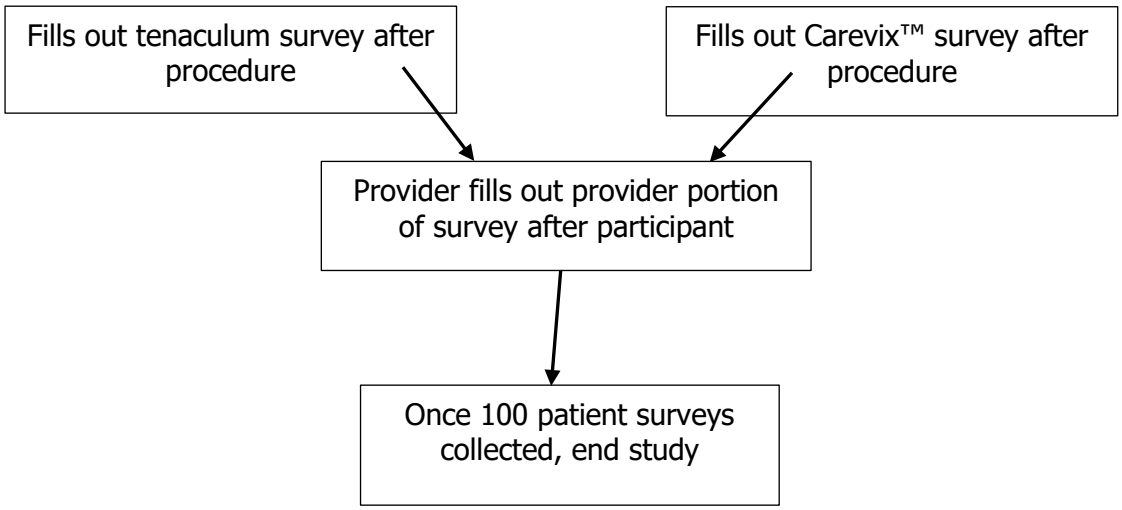
increasing our sample size in this trial to 100 patients (50 in each group), the power increases to 94% for detecting the same 1.64-point difference in pain scores.

In the pilot trial, we assessed pain scores at only 2 points: at cervix grasping and at completion of the procedure. In the European trial, they analyzed pain at 7 different points during the procedure. We will expand our pain assessment to include: **at baseline** (prior to any examination or procedure and expectation of pain), **at cervix grasping**, **at cervix traction**, and at **completion of the procedure**. This study will utilize the NRS pain scale, a pain screening tool commonly used to assess pain severity at that moment in time using a 0–10 scale, with zero meaning "no pain" and 10 meaning "the worst pain imaginable".[8] The patient will be asked their baseline pain score (0-10) prior to getting undressed for the procedure, they will be asked their expectation for pain at this time as well, and then the provider will ask the patient's pain score at cervix grasping with either the device or tenaculum, and at cervix traction prior to IUD insertion. The patient will then fill out their own pain score only at conclusion of the procedure after they have gotten dressed while they are filling out their survey questions.

Following completion of their procedure, the patient will fill out the survey (attached) asking their demographics and about their experience, which takes about 1-2 minute to complete. The provider performing the procedure will finish the survey with provider-specific questions about bleeding, ease of use and satisfaction. The purpose of this study is to compare Carevix™ to the tenaculum and determine if the Carevix™ shows similar results in the United States population as it has in the European study and with IUD insertions.

Flow diagram for randomized study





6.0 Enrollment

We intend to enroll one hundred patients who are presenting for IUD insertion at participating IU Health clinics throughout the state of Indiana. All patients presenting for IUD insertion to participating clinics at IU Health who meet inclusion criteria will be approached for this study. If a randomized participant has a post-randomization exclusion, most likely due to a listed cervical condition or anomaly on the exclusion list, they will be replaced with a new recruit but accounted for in the total enrolled participant report.

7.0 Study Procedures

IUD insertions already scheduled will otherwise proceed accordingly as part of clinical care. During the enrollment, patients who fit above inclusion criteria and are scheduled for an IUD insertion will be approached about this study and guided through an informed consent process and provided with a copy of their signed ICF during the recruitment period.

Following completion of the procedure, the patient will then fill out the patient-based survey. Following the completion of the patient's questions, the provider will then fill out the provider-based survey.

The survey will be done on paper and entered into REDCap as a secondary source for documentation for HIPAA and FDA 21 CFR Part 11 compliance and data security.

8.0 Study Calendar/Timeline/Use of results

There is no specific study calendar – the patient will have their IUD procedure scheduled and will decide if they wish to participate in this randomized trial or not. The event will be a one-time procedure only occurring during and immediately after their IUD insertion procedure. There will be no follow-up planned.

The timeline is that recruitment will start shortly after funding is granted, and we anticipate less than 1 year for study recruitment completion.

The intention of this project is to determine if the use of Carevix makes IUD insertions less painful than using the standard tenaculum.

9.0 Reportable Events

It is not anticipated that there will be Serious Adverse Effects as defined by the FDA (death, life-threatening complications, need for hospitalization, disability or permanent damage, or an intervention needed to prevent permanent impairment or damage). However, if one occurs, it will be promptly reported to the IU IRB and sponsor (within 5 days of knowing about the occurrence) and per IU HRPP policy if unexpected, related/possibly related to participation and if the SAE suggests that the research places the subject or others at greater risk of harm. Study staff will document adverse events and the Principal Investigator will assess whether they are anticipated, related or possibly related to the procedure, and placed subjects at greater risk of harm. All unanticipated adverse device effects (serious and not serious) will be promptly reported to the IU IRB.

Other adverse events (AE) that may occur with any cervical stabilization device, such as bleeding or injury at stabilization site needing medication or surgical intervention, are uncommon and will be collected and reported as part of study data and at annual regulatory reviews. In the European trial, providers reported no bleeding in 89% (42 of 48) of subjects compared to tenaculum (40% or 21 of 52). Bruising was more common in the Carevix™ group (16%, or 8 of 48 participants), and no bleeding events required more than management with silver nitrate. Definition of an adverse event for bleeding will be: requiring any intervention beyond direct pressure or silver nitrate (such as suturing).

10.0 Data Safety Monitoring

This study is no greater than minimal risk. Data safety and monitoring will be performed by the database manager for the REDCap database and the PI. Data quality, subject recruitment data completion, outcome and adverse event data, and proper consent procedures will be regularly reviewed by the PI, study coordinator, and data manager at least monthly. A formal Data Safety Monitoring Board is not required. While no formal stopping criteria are proposed, monitoring of AEs will be ongoing and will be discussed by the PI and Department representatives if the AE rate (notably bleeding or injury to the stabilization site on the cervix) is above 50%.

11.0 Study Withdrawal/Discontinuation

Patients can decline participation and will receive standard of care (tenaculum) if cervical stabilization is required. Patients who consent to participate in the randomization trial and who require no cervical stabilization or are

assessed by the provider to be otherwise ineligible for the device will be considered ineligible and will still be asked to fill out the survey as per intention-to-treat analysis.

12.0 Statistical Considerations

We performed sample size/power calculations with the primary outcome of pain (visual analog scale) at the time of Carevix™/tenaculum use. For our pilot study analysis, we used the Wilcoxon test instead of the t-test because the data were not normally distributed, with generally left shifted data (lower pain scores). Since the Wilcoxon test does not rely on the normality assumption, we used a simulation approach to estimate the power rather than the t-test power analysis. With the pilot trial dataset, we have 44% power to detect a 1.64-point difference in pain scores. If we increase the sample size to 100 patients (50 in each group), the power increases to 94% for detecting the same 1.64-point difference in pain scores. We conducted our power simulation in R using a lognormal distribution to approximate the distributions we observed in our pilot data. We used rlnorm() with the parameters mean = 1.26 and sd = 1.28 for the Carevix group and mean = 2.9 and sd = 2.88 for the Tenaculum group. We generated 50 samples per group for each iteration, performed a Wilcoxon test at $\alpha = 0.05$, and repeated this process 10000 times. The proportion of simulations with $p < 0.05$ was then used to estimate the empirical power. This will be the basis for our current analysis.

Descriptive characteristics of those in the Carevix™ and control groups will be compared using standard statistical testing such as Chi-square and t-tests. We will once again assess for normality of the data in this study and will use appropriate tests for comparisons, such as the Wilcoxon, as we did in the pilot study. We anticipate the need for using nonparametric testing. Our department has a partnership with the Department of Biostatisics, who assisted with the pilot analysis, this sample size calculation, and will be responsible for the randomization scheme and ultimately the final data analyses. They will utilize R for their data analysis. Differences in outcomes between the device and control groups will similarly utilize standard testing. We will compare the subgroups of nulliparous and parous participants separately to assess for possible differences in two groups, similar to what was seen in the European study. We will examine some covariates to assess their potential effects in both groups. For continuous outcomes, such as pain score, we plan to use the generalized linear model (GLM). This method allows us to evaluate the main effects or potential interaction effects on the outcome. While we anticipate that randomization will lead to similar demographic characteristics in both Carevix and tenaculum groups, if significant differences occur by chance, we will consider other adjusted analyses as needed.

13.0 Statistical Data Management

Individual research data will not be made available to the clinical care provider. Primary data will be collected via paper surveys and then electronically stored in REDCap, SAS files, and excel spreadsheets on encrypted secure servers. Quality assurance steps may include: 1) built in range check; 2) defined user definitions; and, 3) testing of

database integrity by study team members prior to commencing statistical analyses. The following quality control methods will be used: 1) single entry, with random checks of accuracy; and, 2) extraction and cleaning of data that will be used for analysis as needed. Survey data collection will be done in person via paper surveys. Consenting will occur in person on paper ICFs and CRFs in a private room. The signed consent forms will be stored in a secure and lockable cabinet.

14.0 Privacy/Confidentiality Issues

This is a comparative effectiveness trial posing no more than minimal risk of loss of privacy and confidentiality. Consent will occur in person during gynecological clinical visits. All participants will be assigned a unique participant ID number to link patient and provider questionnaires. Paper documents will be stored in a lockable file cabinet within a locked room with limited access to qualified members of the research team. None of the questions on the data collection questionnaire will contain PHI. Study questionnaires will be administered in person via paper surveys and then stored electronically on REDCap during a gynecological clinical visit within a private area. Data will be stored in a lockable cabinet and electronically on REDCap. Study outcomes (abstracts, presentations, publications, media interviews, etc.) will use only aggregate data, and will not disclose individual participant data.

15.0 Follow-up and Record Retention

The study will last about 1 year. We will keep the data in accordance with the IU HRPP policy on research data management.

16.0 References

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1.0 Appendix

Attachment #1: Aspivix company brochure on Carevix™
Attachment #2: Carevix™ data published in the journal *Contraception*.
Attachment #3: Questionnaire for patients and providers (done through the same link).
Attachment #4: Study information sheet and consent form.
Attachment #5: Our pilot data from 2024 trial on all intrauterine procedures
Attachment #6: CDC updated recommendations for pain management during IUD insertion 8.8.24