Side effects of Mirena® and Paragard® IUD usage in nulliparous women

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A) Study Purpose and Rationale

This study is designed to analyze the two IUDs that are available in the United States, Paragard® and Mirena®, looking specifically at side effects in nulliparous women. IUDs are used relatively infrequently in this population, especially in the US, partly because of fear of complications such as perforation and infertility. This fear exists not only within the population itself, but also amongst obstetricians/gynecologists. A study in the UK demonstrated that only 2% of clinicians would recommend an IUD in a nulliparous 19 year old.[1] In a US survey on 400 fellows of the American College of Obstetrics and Gynecology, 68% said they would not recommend the IUD in nulliparous women.[2]

The uncertainty regarding usage in this female demographic is not surprising considering that until 2005 Paragard® was only recommended in women with a history of childbearing, and the Mirena® package insert still recommends having had at least one child before insertion. The IUD has been classified as category 1 for women who have had a child and category 2 for nulliparous women, demonstrating the discrepancy in use amongst both types of women.

Part of the reason for this discrepancy is the lack of research which has been done comparing side effects between nulliparous and parous women, specifically looking at the risk of perforation, one of the worst side effects, and also discrepancies between Mirena® and Paragard®.[3] There have been many studies analyzing certain risk factors in parous vs nulliparous women, however these studies are often retrospective, small, and not applicable to the population at large. For instance, side effects of the IUD in nulliparous women were studied by Duenas et al; however, he looked at a population with stable sexual partners (so PID did not occur in any participant) who had their uterine size and cervical size measured prior to insertion to ensure adequate uterine size (which would likely decrease the rates of expulsion and perforation).[4] Another study retrospectively looked at side effects of IUDs, but the study only looked at 129 nulliparous women, therefore giving it insufficient power to detect many of the rare side effects like perforation.[5]

Not only is there minimal information regarding side effects of IUDs in nulliparous women, but also there is no accurate data comparing the two types of IUDs in this population. The Paragard® is a type of copper IUD, and is also referred to as TCu380A. It contains a T shaped polyethylene frame with a fine copper wire round around the stem and copper collars on each arm. There is a 3 mm ball at the base which functions to decrease the risk of perforation.

The Mirena® consists of a T shaped polyethylene frame with 52 mg of levonorgestrel dispersed in polydimethylsiloxane, which is attached to a vertical stem. It is designed to release 20 mcg of levonorgestrel daily, which serves to locally affect the uterus without systemic involvement. Both IUDs have very low failure rates (Paragard® Is 1.6% at 7 years, while Mirena® is 1.1% in that same time period. [6][7]

Therefore, this study aims to analyze side effects in nulliparous vs parous women and women with the copper IUD vs levonorgestrel IUD. It will look primarily at perforation, but it will also assess expulsion, PID, bleeding and pain on insertion. Ideally the study will be large enough to

confirm whether or not there is a difference in the risk profile of IUDs in nulliparous vs parous women, and whether one IUD is better in this population than the other.

B) Study Design and Statistical Analysis

This study will be a cohort study looking at 22,000 women with placement of IUD (11,000 nulliparous and 11,000 parous). This number was determined using the chi squared analysis to obtain a power of 80%, with a type I error rate of 0.5, as the presumed risk of perforation is approximately 1.3%, and is the least likely side effect.[2] Due to the smaller uterine size of nulliparous women, I would imagine that there would be a slightly higher rate of perforation as well as expulsion, with a rate of perforation at 2%. Letters will be sent to obstetricians/gynecologists associated with major hospitals around the country as well as Planned Parenthood organizations requesting participation in the study. If the obstetrician/gynecologist agrees to the study, they will be instructed on how to give the appropriate informed consent, and they will be distributed study consent forms for the patients as well as questionnaires to fill out on each study participant. They will be asked to submit all completed consents and questionnaires to the principal investigator bi-annually. The participants will be followed for 5 years (or until removal if before 5 years) for side effects including perforation, expulsion, PID, bleeding, and pain. The 5 years marker was chosen because that is the maximum length a Mirena® IUD can remain in place. If a participant removes a device early, the reason for removal will be recorded. Each side effect will be analyzed individually with a chi squared analysis.

C) Study Procedure

Each participant will be a woman who already intends on using an IUD as her chosen method of contraception. She will also choose whether she wants the Paragard® or the Mirena® IUD. The participant will then have the IUD of choice inserted by her trained obstetrician/gynecologist in the office using standard insertion methods. The insertion should take approximately 30 minutes. The procedure is mildly painful. Any events on insertion will be noted. Repeat procedures are not necessary, except for IUD removal, which will be done at 5 years (for the Mirena®), 10 years (for the Paragard®), or at the patient's discretion. The patient will follow up annually with her obstetrician/gynecologist, and at that time will report any complaints/side effects with the IUD. The participant will also be encouraged to call her clinician at any point that she experiences discomfort. Each clinician will be expected to keep a confidential record of date of insertion, date of removal, and date/description of any complaints or events in between. In order to obtain an adequate number of participants, an estimated length of the study is 10-12 years.

D) Study Drugs

N/A

E) Medical Devices

Participants will be obtaining the commercially available Paragard® or Mirena® IUDs. Both IUDs have been thoroughly studied as safe and effective birth control methods. They are widely used internationally (accounting for approximately 13-50% of international contraception); however, in the US they are used by only approximately 5.5% of contraception users.[8] Contraindications of an IUD include: Pregnancy or suspicion of pregnancy, abnormalities of the uterus resulting in distortion of the uterine cavity, acute pelvic inflammatory disease, or current

behavior suggesting a high risk for pelvic inflammatory disease, postpartum endometritis or postabortal endometritis in the past 3 months, known or suspected uterine or cervical malignancy, genital bleeding of unknown etiology, mucopurulent cervicitis, or Wilson's disease. Serious side effects include ectopic pregnancy, perforation, PID, and expulsion. Less severe side effects include dysmenorrheal, menstrual spotting/prolonged flow, pain/cramping, or vaginitis.

F) Study Questionnaires

Data will be collected by obstetricians/gynecologists or women's health clinicians who will be inserting the IUDs. These physicians must be trained on how to insert the device, and they must be able to recognize side effects. They will be given a questionnaire to fill out on each patient, with information concerning age, parity, race, ethnicity, date of insertion, date of removal, pain level on insertion (0-10), perforation (y/n), PID during 5 year period (y/n), excessive bleeding (y/n), and reason for removal. There will be a place for comments/reported patient complaints at the bottom of the page.

G) Study Subjects

Study Inclusion criteria is female, desiring IUD for contraceptive purposes, age 18-40. The woman should not have a history of previous IUD usage, PID, or abdominal/uterine/vaginal surgery. Women who have had abortions will be excluded from the study due to potential previous uterine damage, as should women with leiomyomas. Women for whom IUDs are contraindicated will obviously not be included. Patients must be able to give informed consent to the study and placement of the IUD.

The women should ideally be demographically mixed, representing multiple racial and ethnic groups. All physicians will be required to speak English in order to fully comprehend the questionnaire; however, participants can speak non-English languages as long as informed consent is obtained in the language of their choice.

H) Recruitment of Subjects

Potential subjects will be recruited from the community by their obstetricians/gynecologist when they specifically come in requesting an IUD or when they come in requesting contraception, are explained all viable options, and decide on the IUD. The physician must agree that the patient is suitable for the study and must ascertain that the patient is willing to consider participating in the study before the study is officially discussed. After discussion, the physician or clinical study coordinator can explain the study to the patient using language that could be understood with a 4^{th} grade education level in order to obtain appropriate consent.

I) Confidentiality of Study Data

The study forms and consent materials as well as the questionnaires will be kept in locked file cabinets in the physicians' office. Names will not be used, but rather each questionnaire will have numbers on top (1 to 22,000) and each physician is responsible for keeping the name that corresponds with the code within the locked file cabinet.

Consents/Questionnaires sent to the PI will be kept in locked filing cabinets in number order based on their codes. The sheets that reveal each identity associated with the coded number

will not be sent to the PI. The data analysis will be performed on an encrypted computer network and will be password protected.

J) Potential Conflict of Interest

All clinicians who are being compensated by the manufacturers of Paragard® or Mirena® must disclose that information prior to participating in the study.

K) Location of the Study

The study is a multi-center clinical trial, and will be utilizing obstetricians and gynecologists from hospitals and Planned Parenthoods around the country. The study will gain approval at every institution's IRB prior to initiation.

L) Potential Risks

The risks to each subject are going to be the same as those experienced during any insertion of an IUD. For complete listing of risks/side effects, please see "Medical Device" section.

M) Potential Benefits

The subject will not benefit as a result of their participation in the study; however, there will potentially be a huge benefit to society by encouraging nulliparous women to use IUDs and clearly identifying which IUD would be most beneficial in this population.

N) Alternative Therapies

N/A

O) Compensation to Subjects

Compensation will not be provided to subjects.

P) Costs to Subjects

The subject will not incur any additional costs as a result of participating in the study

Q) Minors as Research Subjects

N/A

R) Radiation of Radioactive Substances

N/A

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