

Study Title: A cluster randomized trial of a home-based intervention to increase uptake of postpartum contraceptives and its effect on short-interval pregnancy rates in a postpartum population of rural Guatemalan women

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Summary: This study will involve a home-based intervention to increase uptake of contraception, especially the contraceptive implant, Jadelle®, in a postpartum population in the SW Trifinio region and document how increased uptake affects short-interval pregnancy rates. All contraceptives involved are already in common use in the population.

Problem: Adolescent pregnancy, high fertility rates, and high unmet need for contraception are a significant health sector problem for Guatemala, a Central American country, and are the public health problems of interest in this study [1]. According to the Guttmacher Institute, 11% of Guatemalan females are adolescents (age 15 – 19), 30% report having their sexual debut within this age range, and 22% of them have been married [2]. This study will focus on a sub-population (women age 15 – 35) of women from the rural Southwest (SW) Trifinio region of Guatemala who, according to a needs assessment and several program evaluation studies of the population, are particularly burdened by high fertility rates, high unmet need for contraception, and adolescent pregnancy [1]. The average birth spacing interval in this population is unknown [1]. Four percent of patients currently opt for Jadelle® as their birth-spacing method of choice, and the reported pregnancy rate in this group is unknown [1].

Significance and Use of Results: The previously mentioned research details the experience of North American populations living in a high-income country with access to healthcare resources. The objective of this research proposal is to study how improving access and delivery of contraception postpartum, by providing it in the home setting, can increase postpartum contraceptive uptake and reduce repeat pregnancy among a high-risk Central American rural population of women. No studies currently exist in the literature on interventions to increase postpartum contraceptive use in Guatemala. Information gleaned from this study will be used to learn more about the study population and subsequently perform additional studies aimed at increasing postpartum contraceptive use.

This study will first address the question of whether provision of contraceptives in the home setting can increase uptake, especially of the postpartum implant Jadelle® in the population of interest. Second, it will observe whether or not the continuation rates and success seen with implant use in Northern American populations can be replicated in a Central American population. Third, the study will observe how acceptable the device is to the study population as

well as how manageable it is to supply and administer such devices in a rural, low-resource setting. And fourth, the intervention should increase knowledge regarding the effect of implant placement on short-interval pregnancy rates. As LARC implants are already widely used in HIC settings with, according to the WHO, minimal risk and significant benefit, we believe the importance of the knowledge gained in relation to the risk/benefit ratio favors performing the study intervention.

Background: Repeat short-interval pregnancies (< 12 months) are more likely to be complicated by preterm birth, stillbirth, maternal reliance on public assistance, termination of maternal education, and high subsequent parity [3]. A large proportion of attributable risk for major perinatal morbidity and mortality is related to short-interval pregnancy in the North American population [3]. While it is likely that there are similar attributable risks in other populations, there have been limited studies.

One method of preventing short-interval pregnancy is to encourage contraceptive use in the postpartum setting. Long-acting reversible contraceptive (LARC) methods provide effective contraception for an extended period without requiring user action; LARC generally includes intrauterine devices (IUD) and implants [4]. LARC, and in particular implants, have been shown to be highly effective in preventing rapid repeat pregnancy (< 12 months) [3].

Different methodologies have been used to try and increase uptake of contraceptives in the postpartum setting. One study looked at the provision of contraceptives in the home, and found that clients had less days not covered by effective contraceptive use during the 90 days following a first birth [5]. The authors suggested that home dispensing of hormonal contraceptives may improve women's postpartum contraceptive use and should be explored as an intervention in communities where contraceptives are not easily accessible [5]. This study design did not include offering LARC in the home.

A research group from the Department of Obstetrics and Gynecology at the University of Colorado wanted to observe the actual clinical impact that such LARC devices might have on repeat pregnancy and contraceptive continuation rates among adolescents [3]. They conducted a prospective observational study of immediate postpartum implant insertion and found a 2.6% pregnancy rate one year post-placement, compared to an 18.6% pregnancy rate among the control group [3]. Their research shows that high continuation rates of postpartum LARC can translate into reduced immediate postpartum pregnancy rates. Downstream benefits of using LARC in this population also appeared to include a 2-percentage point decrease in preterm birth, which was an unexpected but highly beneficial outcome [3].

This study combines the two prior aforementioned study in a new population; it desires to look at home-based provision of contraceptive care, including LARC in the form of the progesterone-only implant called Jadelle®, and observing how this reduction of a barrier to access increasing uptake of all contraceptives, including abstinence. The hypotheses are:

Hypothesis 1: Offering routinely available contraceptives in a home setting can increase incidence of contraceptive initiation in a postpartum rural Guatemalan population.

Hypothesis 2: Increased use of long-acting reversible contraceptives placed in the home setting in a rural, postpartum Guatemalan population will decrease short-interval pregnancy rates.

Research Objectives: This study has the following objectives:

Objective 1: Increase uptake of routinely offered contraceptives in the postpartum setting by providing them to women at their home-based postpartum visit.

Objective 2: Determine short-interval pregnancy, satisfaction, and continuation rates among women who received contraceptives in the home versus those that sought postpartum contraceptives through routine care.

Objective 3: Determine short-interval pregnancy, satisfaction, and continuation rates among women who opted for long-acting versus short-acting reversible contraceptives that were provided in the home setting.

Objective 4: Document side effects and adverse events occurring in the study population.

Methodology:

Study Design: This study is a cluster randomized trial of an intervention to increase uptake of postpartum contraception by providing them to women in their home and observe the effect on uptake in the community of interest. We have eight communities involved the healthcare services provides by the CHD that will be combined into six clusters, for study purposes. The clusters are independent of one another, except that some nurses offering the contraceptives may cover more than one cluster. Patients may also move between clusters over the course of the trial. Women will be recruited for enrollment into the CHD, and subsequently the study, blind to whether their cluster will be offered home-based contraception in the postpartum setting.

Operational Definitions/Proposed Intervention: This is a prospective community cluster-randomized study of a home-based intervention to increase uptake of postpartum contraceptives and study the direct effect on short-interval pregnancy, continuation, and satisfaction rates. The study has two phases.

Phase 1: The first phase fulfills AIM 1 and will involve a cluster randomized trial of the intervention, which is to bring and offer Jadelle[®], among all other routine postpartum contraceptive options, to the women in their homes, compared to routine care. Currently, around 4% of the population opts for Jadelle[®], which is less than expected, likely due to the fact that previously, Jadelle[®] was only offered

at a clinic inconvenient to the study population that required significant time and travel costs. Recently, implant availability has increased in the region due to the work of a non-governmental organization, and the nurses within the CHD were trained on implant placement. Therefore, Jadelle®, which was previously offered as part of the standard of care but not routinely available, now is accessible.

Based on previously collected data, we expect that during our study timeframe around 260 women will meet eligibility criteria over the course of one year. The clusters will be randomly assigned by a biostatistician. This study, with 200 women enrolled (100 from intervention clusters and 100 from control clusters) will be powered to detect a change in Jadelle uptake rates from 3% to 15% at 85% power and 5% significance, with an intra class correlation of 2%.

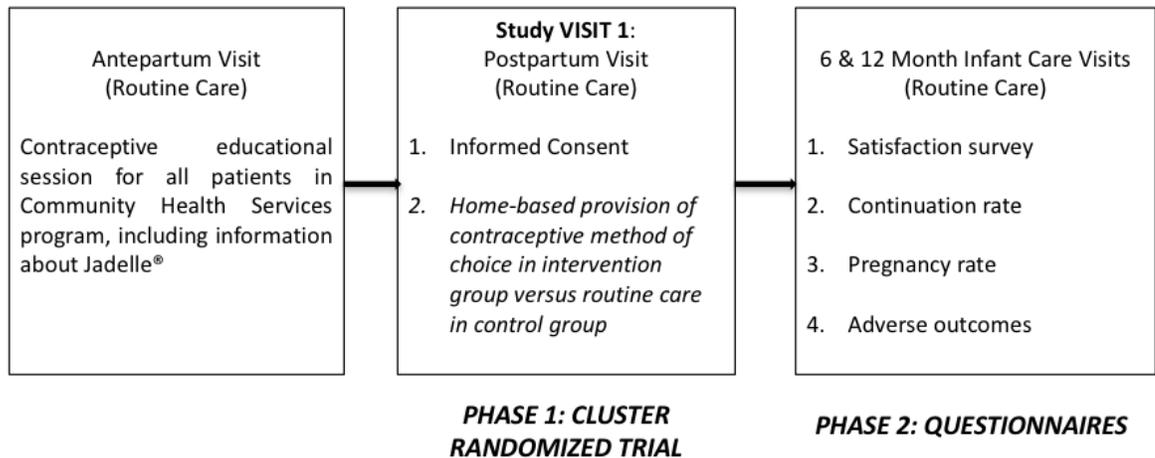
Group	Proportion Positive	N Per Group	Standard Error	95% Lower	95% Upper
Population 1	0.03	100			
Population 2	0.15	100			
Rate Difference	-0.12	200	0.04	-0.20	-0.04

Alpha= 0.050, Tails= 2, Power = 0.848

Power computation: Normal approximation (unweighted mean p)
Precision computation: Log method

Phase II: Phase two of the study are six month and one-year follow-up visits that occur as part of routine care. Patients are immediately enrolled on delivery into Ninos Sanos, the early childhood health and development program offered through the CHD. Women and infants are seen monthly as part of the program, including routine visits at six and twelve months. At these sessions, mothers will be subject to a questionnaire regarding their contraceptive satisfaction and continuation habits, as well as whether or not they became pregnant since their delivery. This frequent and routine contact will ensure that patients are easily located for performing the follow-up questionnaire, but also will have no problem contacting study personnel if they have issues with their contraception or to report adverse events. We will also hold a focus group (interviews and surveys) for providers regarding their comfort and satisfaction with provision of care in the home setting before the study begins and after enrollment is complete.

Study Flow Diagram:



Study Visits: Patients who participate in the Community Health Services program through the CHD receive routine antepartum counseling on postpartum contraception in their home. At this visit, which is part of routine care, all women receive an educational intervention on contraception, which includes Jadelle® and the risks/side effects, benefits, and alternatives to the immediate postpartum implant.

Visit 1: At the postpartum visit in their home, patients will be enrolled in the study and provide informed consent. Once they have agreed to participate in the study, they will be offered postpartum contraception in the home in the intervention group, and through routine care (at CHD pharmacy or clinic location) in the control group. The nurses will bring all routinely available medications to the patient's home for those in the intervention clusters, including pills, condoms, Jadelle®, and depot medroxyprogesterone acetate. Patients who are breastfeeding will not be offered estrogen-containing methods. Participants in both the intervention group and control group will also be offered IUD placement; regardless of group, they will need to present to an area clinic setting for placement should they choose this method. Women opting for Jadelle® will receive immediate implant placement, and women that opt for other methods will receive their method of choice. 99% of patients in the community service program are seen for this postpartum visit, which is part of the standard of care for patients in this region.

Ninos Sanos Visits: The follow-up visits will occur through routine care as part of the Ninos Sanos program, into which all patients in the Madres Sanas program are automatically enrolled. Mothers are seen with their infants monthly in their home, including visits at six and twelve months after delivery. At these routine visits, the mothers enrolled in the study, in both groups, will complete a survey. The surveys will assess patient continuation rates and satisfaction with the contraceptive method of choice. Patients will also be queried about side effects such as: irregular bleeding, weight gain, headaches, rash, chest pain, moodiness, insertion site pain, cramps, acne, nausea, hair loss, or issues with breastfeeding after device placement. All patients will be questioned regarding repeat

pregnancy at these visits, as well, including outcomes of repeat pregnancies such as delivery, termination of pregnancy, or spontaneous abortion. We anticipate that this survey will take about 10 – 20 mins to administer. Additionally, the study nurses will perform a survey of their comfort and satisfaction with administering contraception in the home, which will be performed after enrollment is complete. These questionnaires are included with the submission.

Unscheduled Visits: Unscheduled visits may occur if patients wish to be evaluated for side effects attributed to the implant or for implant removal.

Study Population: The study will be performed in the SW Trifinio region of Guatemala by the Center for Human Development (CHD), a partnership between Agro-America and the Center for Global Health (CGH) at the Colorado School of Public Health (CSPH). The study will be conducted within the current research infrastructure of the CHD and will involve assessments of patients at an antepartum visit, postpartum visit, and one year postpartum. Inclusion and exclusion criteria are outlined in the table to the right. No restrictions will be made based on pregnancy criteria; the only requirement is that patients be participants in the Madres Sanas community program offered by the CHD and already have been enrolled in the database.

Inclusion & Exclusion Criteria:

Inclusion Criteria:
1) Pregnant young women (age 15 – 35) in the CHD community health services program
Exclusion Criteria:
1) Active psychosis or altered mental status; must be able to provide informed consent
2) Unwilling or unable to participate in all study procedures

Procedures for Data Collection & Quality Control: The maternal community nursing program (Madres Sanas Program) that exists within the CHD focuses on improving prenatal care, screening pregnant women for complications, establishing a referral system for high-risk pregnancies, and shifting to facility delivery from home deliveries [6]. The Madres Sanas program uses a home visiting prenatal and newborn care model with community health nurses (CHN) who deliver four prenatal individual or group prenatal care visits, as well as an assessment of the mothers in their immediate postpartum periods [6].

The nurses enter visit data on mobile devices into the prenatal clinical quality improvement database in REDCap, which allows health information and outcomes on women to be monitored during and after pregnancy [6]. REDCap is a secure, web-based application designed to capture and store health research data. It is HIPAA compliant, compatible with several statistics packages, and easy to use. REDCap is designed to export data for analysis and reporting, and therefore does not include these capabilities. It resides on the University’s secure server and is accessed via the internet. It is auto-encrypted and requires logins and passwords. User accounts are controlled by the REDCap administrator and access to individual databases is controlled by the owner of the

database, CHD. There is the ability to create a comprehensive audit trail, create metadata, and validate data.

The community health nurse, who is a native Spanish speaker will explain the study in Spanish based on a prepared script. Extensive discussion of study procedures, risks, and possible benefits of the implant will be provided to the subjects. It will also be explained that the consent allows us to access data collected through the pregnancy registry and child development programs thus minimizing the need to duplicate questions/data to the patient as well as data collected through the medical record. Potential subjects will be given a copy of the consent to read or will have it read to them if unable to read. The subjects will have the opportunity to discuss the research study with their family and/or friends and think about it prior to agreeing to participate. The study team member will then ask the mother if they have any questions about the study and if they understood everything that was said. The nurse will answer all questions. The consent will be completed on paper forms, which will be signed by the mother. A copy of the informed consent document will be given to the subjects for their records while a photo of the paper copy will be uploaded to REDCap for study records. The subjects may withdraw consent at any time throughout the course of the clinical study.

The same community health nurses who collect the database information and provide the clinical care will be trained in the consent, enrollment, and implant placement process for this study. During the postpartum visit, after a woman has completed her routine evaluation, the community health nurse will invite the woman to participate in this study. If she is not interested, it will not affect her involvement in the community program, she will receive care as usual. If she is interested, then the procedure for obtaining consent will be followed. While women can be enrolled in the clinical care database at any point during their pregnancy, the program entails four visits, ideally at <12 weeks, 13-28 weeks, 29-35 weeks, >36 weeks. During these visits information on health and pregnancy history are obtained as well as measurements of weight, fetal heart rate, fundal height, and blood pressure. Community health nurses come in contact with these women multiple ways: word of mouth, self-referral, referral through other CHD programs.

Procedures to Ensure Ethical Research: In order for the study to move forward as planned, it will require approval from numerous ethics organizations. These include the Colorado Multiple Institutional Review Board, the University Francisco Marroquin Institutional Review Board, and the Community Advisory Board for Research from the SW Trifinio region in Guatemala. These multiple levels of review will ensure that the research is culturally appropriate, that researchers are sufficiently qualified and expert to perform the proposed research, that the logistics of the international nature of the project are well planned and executed, and that dissemination of results back to the community is performed.

Patients are consented for this study at the postpartum visit. The patients participating in the cluster randomized trial will participate in a questionnaire at their six month and one year pediatric visits for the infant they delivered at enrollment into the study. Risks involved with the questionnaire are that patients may not want to answer questions about their contraceptive

continuation, satisfaction, and pregnancy rates. They will have the option to leave the study at any point without any repercussions for their clinical care. We will have these questionnaires performed in a private location, in a one-on-one setting to increase comfort with discussing these issues, and patients will also be able to complete the questionnaire privately if they are literate and do not need assistance.

The primary foreseeable risk of all parts of the study is a breach of privacy and/or confidentiality. Study data will be stored securely in REDCap, which is HIPAA compliant and controls access on a study-by-study basis through the use of unique usernames and passwords. REDCap allows data fields to be flagged as identifiers, and investigators will utilize this feature to remove identifiers from datasets, which are exported for analysis.

Utilization of postpartum contraceptives, including placement of the implant how contraceptive use affects short interval pregnancy rates are the specific aims of this study; the study cannot be performed without offering contraceptives, including device placement. Fortunately, these medications are already in use in the study population and are non-experimental methods. Therefore, with proper counseling and informed consent, we believe the risks of the procedure will be acceptable to the patients and their partners.

Analysis Plan:

Methods & Models: The primary outcome of this study is contraceptive uptake rates in the intervention group. This study, with 200 women enrolled (100 from intervention clusters and 100 from control clusters) will be powered to detect a change in Jadelle uptake rates from 3% to 15% at 85% power and 5% significance, with an intra class correlation of 2%.

The satisfaction surveys will be administered at the six and twelve month well-child visits and will primarily assess patient experience with the medications, including side effects, continuation rates, and pregnancy rates. This quantitative analysis will provide direct feedback in terms of real-world use of contraceptives, their success rates, and their acceptability to the patients, which will also provide baseline research for future interventions to address issues surrounding patient choice of and satisfaction with different method of contraception, including the implant.

Programs Used: The analysis plan for this will use summary statistics to describe the patient population as well as the outcomes. We will use Student t (normally distributed variables) or non-parametric medians (non-normally distributed variables) tests for continuous data and χ^2 or Fisher's exact tests (for variables with cell sizes <5) for categorical data. Bivariate analyses will be performed to compare the groups. Variables that are significant ($P < 0.05$) in the bivariate analyses will be included in a logistic regression to determine independent predictors of repeat pregnancy. SPSS statistical software (version 24.0.0; IBM SPSS Inc, Chicago, IL) will be used for all the analyses.

References:

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Timeline: After we have obtained IRAC/COMIRB APPROVAL and Francisco Marroquin University Ethics approval to proceed with the study, we will begin the study. We anticipate the first step of the trial to start January 2018. We expect this to be a 24-month study; the timeline will appear as follows:

Months	Activities
Dec 2017	Training, Jadelle placement refresher course
Jan – Dec 2018	Study Execution: Intervention in 3 study clusters, routine care in 3 study clusters
January 2019	Data analysis
Jan – Dec 2019	Follow-up Questionnaires: all participants
January 2020	Data analysis

Budget: