International Natural Procreative Technology Evaluation and Surveillance of Treatment for Infertility and Miscarriage (iNEST)

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BACKGROUND AND INTRODUCTION

Infertility is a common problem. While most of current clinical research of infertility focuses on in vitro fertilization and related techniques of assisted reproductive technology (ART), some couples do not wish to use in vitro fertilization, or cannot afford it. Natural procreative technology (NPT) is a standardized approach to the treatment of infertility that does not involve ART. NPT incorporates standard infertility treatments (such as clomiphene or progesterone) within a set of standardized application protocols. The goal of NPT is to identify abnormalities of the woman's reproductive cycle (menstrual cycle), and where possible, correct them by medical intervention.(1, 2) An integral part of NPT is teaching women to observe and chart the biomarkers of their fertility (menstrual) cycle, based on changes in vaginal discharge (resulting from uterine bleeding and cervical mucus production). This charting of fertility biomarkers is done according to the Creighton Model Fertility*Care* System (CrM). (3) The CrM has several applications. First, the CrM chart alerts women when ovulation is approaching within the next few days and therefore intercourse is most likely to result in pregnancy, even for subfertile couples.(4, 5) Second, it also gives the physician a record that can be used as a standardized basis for doing diagnostic tests timed in reference to ovulation. Third, the physician can also employ standard medications to enhance ovulation, luteal hormonal production, or cervical mucus production, and use the CrM chart to assess the immediate response of the woman to treatment. Where appropriate, NPT may also include medical treatment for male factor infertility, and for prior miscarriage. A CME-accredited NPT training course has trained many physicians to apply NPT in their practices. Formal evaluation of the outcomes of NPT in medical practice has been limited to a few studies based on single medical practices.(6-9) We plan to conduct a multi-national prospective observational study to measure the generalizability of this program to multiple populations and settings, and characteristics of patients that may correlate with the likelihood of treatment success.

OBJECTIVES

This is an exploratory study rather than a hypothesis testing study. This study aims to determine what the live birth rates are over time for patients who are treated with natural procreative technology (NPT) for infertility or history of spontaneous abortion, and how the live birth rate may vary by patient characteristics, especially the age of the woman, prior pregnancy, and underlying diagnoses. Secondary analyses will explore outcomes of conceptions (live birth versus other outcomes) and the association of environmental exposures with infertility. This is an observational study: there will be no intervention. Patients will receive whatever care they choose to receive. Couples receiving NPT treatment will be compared to those declining NPT treatment, waiting for NPT treatment, receiving other treatment, or stopping treatment. Interventions received, conceptions, and outcomes of conceptions will be followed for up to 3 years for each couple entering the study.

PATIENT SELECTION CRITERIA

Couples eligible for this study will be all couples who are considering NPT treatment to help them conceive or maintain a pregnancy and who present to participating physicians or other providers during the time of their participation in the study. This study will be conducted through physicians or other licensed clinical providers offering NPT treatment for infertility or miscarriage in the United States, Canada, UK, Ireland, and Australia, with the potential for expansion into other countries as well.

Subject Reimbursement
A couple will be reimbursed $20 for each annual update questionnaire (one each for the woman and the man), $10 for each complete exit questionnaire (one each for the woman and the man), and $20 for each complete pregnancy outcome questionnaire. Couples who are already in the study at the point when reimbursement begins will not be reimbursed retroactively for their participation, but they will be reimbursed for any questionnaires completed going forward. There will be no costs to the couples for their participation in the study, other than the use of their time to speak periodically with study personnel and to fill out the questionnaires.

Clinical Site Reimbursement
Participating clinics will receive $5 per cycle chart that is complete and submitted to the iNEST Study Coordinating Center.

DESIGN
This is a prospective cohort observational study. Couples presenting for possible treatment with NPT will be recruited for participation in the study. Observation of the characteristics of the couples, the nature of the NPT treatments, and the outcomes including live births will be followed for up to three years for each couple entering the study. Data will be collected in three ways:

1) Questionnaires will be obtained from each of the participating couples (separate men's and women's questionnaires) at entry and on an annual basis thereafter for up to 3 years. Whenever a pregnancy is identified, the woman will complete a pregnancy questionnaire. When a couple finishes the study, both the woman and the man will complete an exit questionnaire. All questionnaires will be written and may be administered by paper/mail, secure email or web, or telephone by an authorized study representative.

2) Couples will provide copies of the CrM fertility charts for data abstraction.

3) Medical record information will also be used. A subject-specific form for abstracting data from the medical record about NPT treatment and outcomes will be sent periodically to the practice to be completed by the physician or provider. This will be in electronic or paper form. Alternatively, copies of medical records may be requested by the study, and the relevant information will then be abstracted by study personnel.

Couples who are eligible and willing to participate will either receive a paper informed consent form or be directed to the online consent option. The paper informed consent form will be reviewed with the couple in detail by the study personnel at the physicians practice. For convenience, the informed consent form will also be available online for potential participants to view, print and agree to. Individuals will have the opportunity to ask questions before they consent. These potential participants will be contacted for final consent by study personnel if they use the online consent option. The online consent will be signed by the person typing their name. Verification of the identity of the person completing the online consent form will be done by a follow-up phone call from study personnel before the person enters the study.

All data collected from the questionnaires and medical records will be entered into a single secure database at the University of Utah, Department of Family and Preventive Medicine. A separate secure data table will contain identifying information about the participants in the study (i.e. name, address, phone number, and identification numbers). The aggregate data will be analyzed by Dr. Stanford, in consultation with co-investigator Dr. Parnell. Dr. Kim will review only de-identified data, and will provide advice and direction regarding the statistics and analytic procedures. He may co-author on reports.

STUDY PROCEDURES

Identification of physicians or other licensed providers who are practicing NPT and will participate in the study will be done through the International Institute of Restorative Reproductive Medicine (IIRRM). The IIRRM is an organization of physicians and other clinicians with an interest and practice in NPT. It includes physicians practicing in the United States, Canada, United Kingdom, Ireland, and Australia. Other countries may also be represented, but all study information will be collected from English-speaking patients only.

Routine clinical care with NPT will be performed by participating physicians or providers in this study. Clinical care or protocols will not be affected by this study. Data will be collected as described above. The procedures for data abstraction and submission will be under the direction of Dr. Stanford.

Study participants will be enrolled only through the participating NPT clinics. Recruitment materials and information regarding the study will be presented using brochures, posters, and web-based information such as a website, Facebook page, and a blog.

The study database has been constructed without any patient identifiers (no name, address, phone number, or identification numbers other than study subject number). Study subject numbers will be linkable to individual patients only within a separate secure data file. The data file will be password protected, and located on a password-protected computer in a locked research area of the Department of Family and Preventive Medicine. Combined results from all centers will be used for the analysis in this study. It will be impossible to identify any individual during the course of the analysis or in the reporting of the results.

STATISTICAL METHODS, DATA ANALYSIS AND INTERPRETATION

The database exists in Microsoft Access. Analyses will be done in Excel (for basis of descriptions), SAS and/or SPSS statistical computer programs. As stated above, data used in the analysis will be aggregate data, and will not contain any individual identifiers. Therefore, there will be no possibility of identifying individual respondents during the analysis or in the reporting of the final results.

<u>Analysis of Main Outcome</u>

The main outcome of this study is the proportion of subjects that had a live birth at various time points up to three years after beginning treatment with NPT, compared to couples who do not receive NPT treatment, or who cease to receive NPT treatment. This will be analyzed by standard lifetable techniques to deal with censored data (i.e., couples for whom pregnancy status cannot be ascertained beyond a certain time period). Cox proportional hazards regression will be

used in an exploratory manner to investigate demographic and medical characteristics (particularly woman's age, prior pregnancy, and associated medical diagnoses) that may be associated with a greater likelihood of successful live birth. The same set of analyses will be repeated for the secondary outcome of conception (clinical pregnancy).

Analysis of Secondary Outcomes

Initially, all secondary outcomes will be analyzed as simple proportions, e.g., of couples who conceived, what proportion had a live birth, spontaneous abortion, or other pregnancy outcome. Where indicated by the initial analysis, supplementary analyses using standard statistical techniques may be employed (e.g., a logistic regression with the outcome of live birth versus other pregnancy outcome).

Sample Size

The sample size is not exact since its size depends upon the total number of patients seen at the participating clinics. At the Utah location, we estimate this will be up to 50 new patients per year. The study as a whole, including all centers, may enroll up to 1000 new patients per year. We anticipate keeping the study open for up to 20 years. We do not have sufficiently reliable information to estimate the variance of the predictor variables (age, prior pregnancy, associate medical diagnoses, and other characteristics) in predicting the primary outcome of live birth. Because this is an observational study of existing treatment, we will conduct interim analyses yearly. Based on the results of the interim analyses, we will consult with the participating physicians, the IIRRM, and all study investigators to determine whether the objectives have been sufficiently met to end the study at that point in time.

ADMINISTRATIVE RESPONSIBILITIES

Recruitment of patients to this study will be the responsibility of the site investigators, who are the physicians (site investigators) providing NPT treatment, or their designated office staff. Written informed consent will be obtained within the physicians' practice or through online consent. A copy of the consent will be given to the patient or available online to print by the patient, a second copy kept on file at the physicians' practice, and a third copy sent to Dr. Stanford (Study PI) at the University of Utah. All site investigators and staff will complete the online research subjects protection training available through the NIH prior to beginning their involvement in the study. Site investigators will obtain local IRB approval before their involvement, where applicable and available.

The primary responsibility for appropriate data analysis of the data belongs to Dr. Joseph Stanford. This will be carried out with the assistance and consultation of Dr. Kim and Dr. Parnell. Data will be entered and managed by research staff working in the Department of Family and Preventive Medicine, University of Utah.

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